Kidney Transplantation in HIV Infection

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Awarding institution:
King's College London

Kidney Transplantation in HIV Infection

THESIS

presented for the

DEGREE

of

DOCTOR OF PHILOSOPHY

in

TRANSPLANTATION, IMMUNOLOGY AND MUCOSAL BIOLOGY

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May 2016

Dedication

This thesis is dedicated to *"Abba Father! Our dear Papa (Mark14:36), for the Lord is good and His love endures forever (Psalm 100:5)"*

I dedicate this work to the memory of my grandparents, Alfred and Muthoni Mungai Gathogo who never had the opportunity to learn how to read or write but inspired and challenged us, their grandchildren, to reach our full potential! This thesis is also dedicated to my loving mother, Eng. Jane W. Gathogo, for championing me in every endeavour I set out to achieve. Thank you for believing in me, for all the encouragement, personal sacrifices and support you have given me all through the years. You set the bar high and a lasting legacy in all your accomplishments as a highly successful Chemical & Environmental Engineer. Thank you to my sister, Ruth M. Gathogo, my best friend - for her unwavering and loving support, it is because of you that I am finally handing my thesis in - I owe my success to you. A special thanks to Aunt Margaret N. Lane – I am most grateful for your unrelenting love, support and wisdom every step of the way - *Githomo nikio funguro* – you were right in saying "Education is Key". Thank you to all my family, and my father – Professor Francis Ndemo, for their ongoing encouragement and prayers and I hope this inspires the young persons following in my footsteps – as I am the first Gathogo to undertake a PhD.

Declaration

I, Esther Nyanganyi Gathogo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: ..E Gathogo.....

Date: .....16/05/2016.....

Abstract

The prognosis of human immunodeficiency virus (HIV) has been dramatically improved over the years owing to more widespread access and earlier use of antiretroviral drug therapy. Consequently, HIV-positive patients are no longer dying from AIDS related illnesses but increasingly are experiencing non-infectious complications such as end-stage kidney disease (ESKD).

The prevalence of ESKD among 7,307 black HIV-positive patients in the UK CHIC cohort increased from 0.44% in 2000/2001 to 1.09% in 2010/2011. Kidney transplantation was increasingly used to treat ESKD. Among those suitable for transplantation, survival on dialysis and post-kidney transplantation was similar (89% and 85% at five years, respectively, p=0.53).

97 HIV-positive kidney transplant recipients were identified in the United Kingdom. Of those that met the study criteria (n=78), 34% received a kidney allograft from a living donor and the median follow-up period was 31 (19, 55) months. Patient survival at 1 and 3 years post-KT was excellent at 97·3% and 94·8%, respectively, and the corresponding graft survival rates were 97.3% and 90.0%. Delayed graft function was encountered in 16 patients (21%), all of whom had received a kidney from a deceased donor. The cumulative incidence of allograft rejection (AR) at 1 year was 58% and 21% among patients on ciclosporin (CsA) and tacrolimus (Tac) respectively. Choice of calcineurin inhibitor (CNI) was significantly associated with AR (hazard ratio for Tac vs. CsA 0.25 [95% CI 0.11, 0.57], p=0.001).

Complex drug interactions complicated post-transplant management of HIV/KT recipients. CNI doses for patients who received ritonavir-boosted protease inhibitor (PI) containing cART were significantly lower throughout the first year post-KT (30~fold for ciclosporin, 100~fold for tacrolimus) compared to those receiving PI-sparing antiretroviral regimens. By week 4 post-transplant, more than half of the patients in both CNI groups had achieved target trough concentrations i.e. 50% Tac vs 57% for CsA. Patients in whom mycophenolate (MMF) concentrations were routinely measured experienced significantly reduced cumulative incidence of latent virus infections, even after adjusting for cytomegalovirus prophylaxis (20% vs 84% respectively, p=0.0001).

In conclusion, these data presented in this thesis demonstrate the increasing burden of ESKD despite the widespread use of cART. Findings corroborate the feasibility of kidney transplantation in HIV-positive patients albeit with a high rate of delayed graft function and allograft rejection. Poor allograft outcomes may have been complicated by suboptimal immunotherapy owing to the pharmacokinetic interactions between antiretroviral and immunosuppressant drugs. The use of tacrolimus may be the preferred CNI for use in KT in HIV-positive individuals, and monitoring of mycophenolate drug concentrations may be beneficial in this patient population.

Acknowledgements

First, I would like to thank my PhD supervisors Dr Frank Post and Professor Graham Davies for first giving me the opportunity to undertake this PhD research programme; their support, guidance and encouragement they have given me over the past 6 years. Over the years, they have pushed me to discover, develop and achieve my potential within research.

I would like to thank patient study ID 100001, the very first HIV infected patient who was admitted onto the ward while I was training in renal medicine in 2007. While taking a medical history, it became apparent what a long journey the patient had been through from being diagnosed of HIV to soon after developing kidney failure due to HIV-associated nephropathy and finally receiving a kidney allograft 6 years later. Post-transplant management was complicated by the multiple and complex drug interactions between antiretroviral and immunosuppressant drugs. This inspired my proposal to Mr John Farrell, Chief Pharmacist to sponsor me to undertake a PhD to study HIV kidney transplantation. I would also like to thank Wendy Spicer, Helen Atkinson, Meera Thacker, Iqbal Desai, Neal Marshall, Shireen Rahhal, Caroline Ashley and Leonie Swaden at the Royal Free Pharmacy Department for their continual support with my PhD research. A special thanks to Dr Sanjay Bhagani, Consultant HIV physician and Dr Mark Harber, Consultant Renal physician who gave me an opportunity to learn about the management of HIV kidney patients in their multidisciplinary clinic. Another special thanks to Professor Margaret Johnson for approving the study and to all HIV physicians including Dr Sabine Kinloch for providing access to their patients at the Ian Charleson Day Centre, Royal Free hospital.

Thank you to all the HIV and renal clinicians, transplant surgeons, pharmacists and nurses who contributed their time and expertise to making this multicentre study a success. I would like to specially thank Dr Rachel Hilton, Consultant nephrologist at Guys and St Thomas' hospital; Dr Jeremy Levy, Consultant in renal medicine at Imperial College London and Dr Rachael Jones, Consultant HIV physician at Chelsea and Westminster – the list is not exhaustive and is outlined in **Appendix C**. Thank you to HIV Pharmacy Association, the Renal Pharmacy Group, British Transplant Society, British HIV Association and the Solid Organ Transplant Pharmacy group for their support in this research.

I acknowledge and thank Miss Sophie Jose for her assistance with: 1) data mining from UKCHIC database 2) performing statistical analyses using the denominator UKCHIC data to determine trends in prevalence and incidence of ESKD and the factors associated with ESKD in HIV infection. I also thank Professor Caroline Sabin for her comments that greatly improved the manuscript for this chapter (**Appendix A**). I would also like to thank Colette Smith and Lucy Campbell both medical statisticians who provided ongoing guidance and teaching on statistical analyses in HIV research. Colette Smith was the coordinator for the Methodological and Statistical Issues in Clinical HIV Research four day short course that I undertook during my PhD training run by the HIV Epidemiology and Statistics Group, Royal Free Centre for HIV Medicine, University College London (UCL) Medical School.

Many thanks to all patients who contributed to this research. It is my hope that the outcomes discussed in this thesis will translate into improved clinical care, to provide hope to HIV infected individuals waiting for a kidney transplant and to restore their quality of life after transplantation. At the point of writing, three healthy and HIV negative babies were born to two HIV positive kidney transplant recipients – 30 years on from the discovery of HIV, this is a testament to the effectiveness of antiretroviral therapy in managing HIV infection.

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Glossary

ABO	Blood group incompatible
cART	Combination antiretroviral therapy
ADE	Adverse events
AR	Acute allograft rejection
ARVs	Antiretroviral drugs
ATG	Anti-Thymocyte Globulin
AUC	Area under the curve
BKV	BK-virus
BKVN	BK-virus associated nephropathy
BPAR	Biopsy proven allograft rejection
C0	Concentration at time zero
C2	Concentration at 2-hours post-dose
C4	Concentration at 4-hours post-dose
C_{max}	Maximum concentration
C_{min}	Minimum concentration
$C_{pre\text{-}dose}$	Pre-dose concentration
C_{trough}	Trough concentration
CIT	Cold ischaemic times
CMV	Cytomegalovirus
CMVN	Cytomegalovirus-associated nephropathy
CNI	Calcineurin inhibitors
CRF	Calculated Reaction Frequency
CsA	Ciclosporin A
CYP450	Cytochrome P450 enzyme
DGF	Delayed Graft Function
eGFR	Estimated glomerular filtration rate
EBV	Epstein-Barr Virus
EMIT	Enzyme multiplied immunoassay technique
ESKD	End-stage kidney disease
FSGS	Focal segmental glomerulosclerosis
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV+	HIV-positive individual
HIV-	HIV-negative individual
HIV/ESKD	HIV-associated end-stage kidney disease
HIV/KT	HIV kidney transplantation
HIV/KTR	HIV-positive Kidney Transplant Recipient
HIVAN	HIV-associated nephropathy

HLA	Human leukocyte antigen
HPV	Human papilloma virus
ICKD	Immune complex kidney disease
INI	Integrase inhibitor
IS	Immunosuppression
IST	Immunosuppressive drug therapy
IVIG	Intravenous immunoglobulin
IVMP	Intravenous methylprednisolone
KT	Kidney transplantation
LC-MS/MS	Liquid chromatography–mass spectrometry
LOCF	Last observation carried forward
LVI	Latent viral infection
MMF	Mycophenolate
MPA	Mycophenolic acid
MPAG	Mycophenolic acid-7-O-glucuronide
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucloside/tide reverse transcriptase inhibitors
PI	Protease inhibitors
PI/r	Ritonavir boosted protease inhibitors
PK	Pharmacokinetic
PRA	Panel reactive antibody
PVN	Polyomavirus nephropathy
pRRT	Permanent renal replacement therapy
SIR	Standardised incidence ratios
SLK	Simultaneous liver-kidney transplant
SPK	Simultaneous pancreas-kidney transplant
Tac	Tacrolimus
TDM	Therapeutic drug monitoring
UK	United Kingdom
WIT	Warm ischaemic time

Chapter 1. Introduction

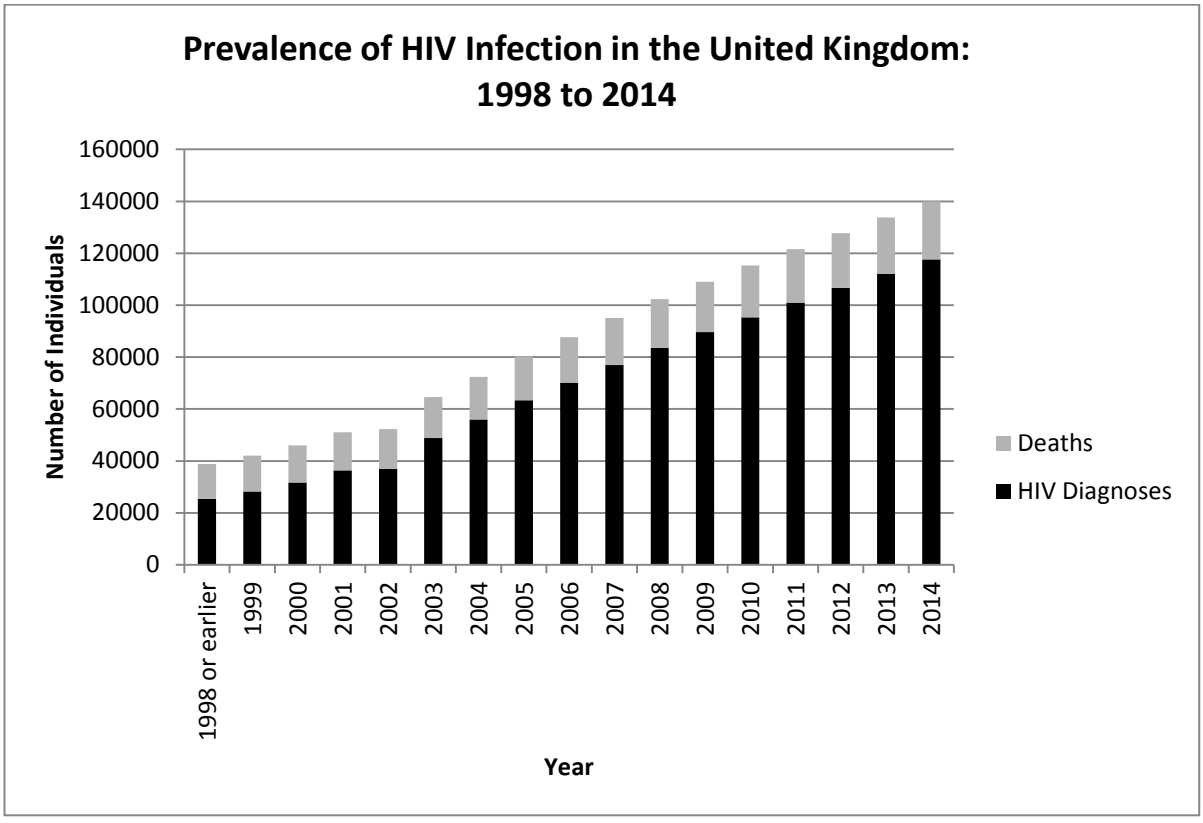
1.1. The Burden of HIV

The global epidemic of the human immunodeficiency virus continues to grow. Since the discovery of the HIV virus there has been an estimated 78 million people infected with HIV. Today, there is an estimated 35 million people living with HIV in the world which is representative of 0.8% of the adult population (age range 15 – 49). The burden of HIV varies between countries with sub-Saharan Africa being the worst affected. It is estimated that 70% of all HIV infected people globally reside in sub-Saharan Africa (UNAIDS, 2013, WHO, 2015a). By 2013, there was approximately 2.3 million HIV infected people living in North American and Western/Central Europe (AVERT, 2013). In Western and Central Europe, the prevalence of HIV is low (0.2%) however, steadily increasing. In 2013 there were 80% more new HIV cases compared to 2004 in Europe (WHO, 2015a).

In the United Kingdom, there is an estimated 107, 800 people living with HIV. The number of new HIV diagnoses has been increasing year on year which is a reflection of the growing prevalence of HIV in the UK (see **Figure 1**). The estimated overall prevalence is 2.8 per 1000 population with majority being male (63%), men who have sex with men (MSM) (40%) and of white ethnicity (48%). By comparison to other European countries, the UK has a low proportion of HIV infected people who have acquired HIV by injectable drug use (HPA, 2014). Of the 114,000 HIV infected people who inject drugs in Western Europe, 2% are from the UK (AVERT, 2013). By contrast, the UK has a high proportion of patients of black ethnicity (42%) compared to other European countries (HPA, 2014).

In 2012, among the new HIV cases that acquired HIV through heterosexual contact in Europe (n=3160) of those who originated from sub-Saharan African countries more than half (58%) were living in the UK (ECDC, 2013). In North America, African Americans are the majority of people living with HIV (56%) (AVERT, 2013).

Figure 1: Trends in HIV Infection in the United Kingdom

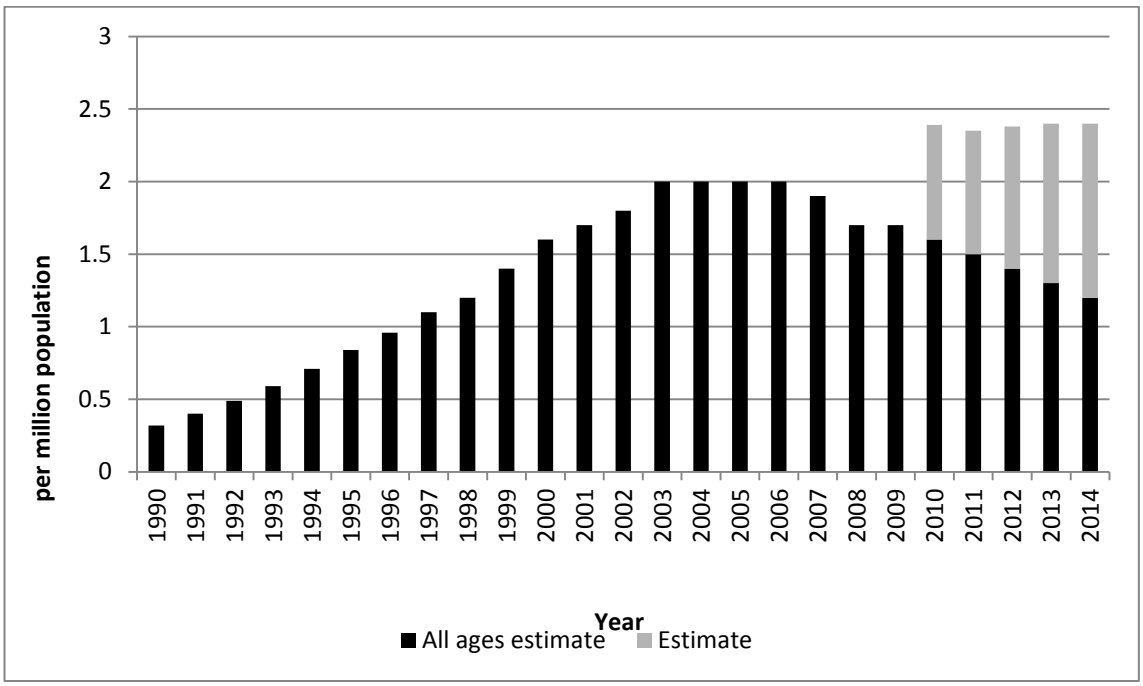


Graph representing the number of HIV infected individuals living in the United Kingdom between 1998 to 2014. Data includes HIV infected individuals accessing HIV care services in the UK, newly diagnosed individuals and number of patients that died year on year. Data obtained from Public Health England Official Statistics: HIV data tables (PHE, 2015b).

The growing prevalence of HIV is suggested to be attributable to the use of antiretroviral therapy which has significantly improved morbidity and mortality. However, despite the wide coverage of antiretroviral therapy, the incidence of HIV has not been impacted in certain groups. A reduction in the incidence of HIV among heterosexuals and in injectable drug users that has been observed is thought to be due to the implementation of effective preventative strategies and programmes. However, the availability of effective antiretroviral therapy is thought to have increased risk behaviour among men who have sex with men thereby increasing the incidence of HIV in this group (Degenhardt et al., 2010, Mayer and Mimiaga, 2011, Beyrer et al., 2013, Birrell et al., 2013, Desai et al., 2013, Zaidi et al., 2013, Maartens et al., 2014).

Since the advent of antiretroviral therapy in the 1990s, the survival of HIV infected people has dramatically improved. In spite of this, HIV/AIDS continues to be one of the deadliest epidemics of the 20th Century (Bongaarts, 2011) (see **Figure 2**). The number of AIDS related deaths peaked in 2005 at 2.3 million but has since declined to 1.6 million in 2012. This decline has been credited to antiretroviral therapy use. From 1996 to 2012, it has been estimated that ART use has averted 6.6 million deaths worldwide (UNAIDS, 2013). About 39% of all HIV infected individuals globally have access to antiretroviral therapy. Of the 12.9 million HIV infected people on ART globally, 11.7 million were from low and middle income countries (WHO, 2015b).

Figure 2: Global Impact of Antiretroviral Therapy on AIDS-related Deaths



Estimated number of AIDS related deaths, with and without antiretroviral therapy, in low and middle income countries between1995 to 2012. Number of deaths due to AIDS-related illnesses (black bars); number of deaths averted due to ART (grey bars). Globally, 15 million people had access to antiretroviral therapy; 9.7 million of those were from low and middle income countries (UNAIDS, 2013).

In the UK, 90% of those accessing HIV care in 2013 were prescribed ART (HPA, 2014). However, even with about one third of all HIV infections globally being managed with ART, AIDS continues to be the leading cause of death in this population. A 12 year longitudinal study (1999 to 2011) using a large HIV cohort (n=49,731) from high income countries found that the proportion of deaths associated with AIDS, liver disease, cardiovascular disease and non-AIDS cancer was 29%, 13%, 11% and 15% respectively (Smith et al., 2014). The AIDS related deaths were associated with uncontrolled HIV virological control, low CD4 T cell count and older age. This emphasises the importance of early HIV diagnosis prior to developing advanced disease and effective HIV treatment with antiretroviral therapy (Scourfield et al., 2011, Smith et al., 2014, Socio-economic et al., 2014). Outcomes from the Swiss HIV cohort study

(n=16,134) over a 22 year period (1988 to 2010) observed an approximated 50 fold decrease in AIDS associated mortality (11.0 to 0.211 per 100 person years respectively). Other important factors associated with risk of death are hepatitis B and C co-infection (Weber et al., 2013). In the United Kingdom, the number of AIDS related deaths declined 3 fold from 2004 (n=1,020) to 2013 (n=320) (HPA, 2014). Majority of the AIDS related deaths were due to advanced HIV disease among people that were diagnosed late. The most common AIDS related illnesses were *Pneumocystis jirovecii pneumonia (32%, 470/1470)*, *Mycobacterium tuberculosis (14%, 200)*, Kaposi sarcoma (9%, 130) and oesophageal candidiasis (9%, 130). The proportion of late diagnoses (CD4 T cell count < 350 cells/mm^3) in the UK represent 42% of those newly diagnosed with HIV. This reflects the need to increase the coverage of HIV testing (HPA, 2014).

The prolonged survival of HIV infected individuals also alludes to an ageing population. In the UK, one in four people living with HIV are over the age of 50 (HPA, 2014). According to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) analysis, the average life expectancy of a 20 year old individual initiating antiretroviral therapy was 51.4 years in 2007; meaning the patient could expect to live to 71.4 years of age (Samji et al., 2013). This is near normal life expectancy which is estimated at 71 years from birth globally and ranging from 66 to 79 in middle and high income countries (WHO, 2015c). With HIV infected people living longer, there is an associated increased risk of non-AIDS related comorbidities such as cardiovascular, renal, non-AIDS related cancers or neurological diseases. Furthermore, there is the risk of drug related toxicities with prolonged use of antiretroviral drug therapy (Gazzola, 2010).

1.2. Management of HIV Infection

Zidovudine was the first antiretroviral drug that was licensed in 1987. Zidovudine is a thymidine analogue, which inhibits the transcription of HIV-1 virus. However, zidovudine as a monotherapy agent proved to be ineffective (Mitsuya et al., 1985, Fischl et al., 1987, Larder et al., 1989, Hammer et al., 1996, Broder, 2010b, Broder, 2010a). In the early to mid-1990s, antiretroviral drugs that targeted different stages of the HIV virus were developed. The rapid turnover of HIV virions and CD4 T target cells made it impossible to eradicate the virus. Furthermore, there was the emergence of HIV viral mutations and resistance to antiretroviral agents. It wasn't until 1997 when highly active antiretroviral therapy (HAART) was used to manage HIV infection. HAART included the combination of three antiretroviral drugs; two nucleoside reverse transcriptase inhibitors as the 'backbone' and a third agent either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. HAART proved highly effective in decreasing viral loads to clinically undetectable levels (<50 copies/mL) (Wei et al., 1995, Gulick et al., 1997, Hammer et al., 1997, Laskey and Siliciano, 2014). The first clinical trial tested the combination of two NRTIs, lamivudine plus zidovudine or stavudine, and one protease inhibitor, indinavir. Study participants were HIV-1 infected, with CD4 T cell counts less than 200 cells/mm^3 and received at least 3 months of zidovudine monotherapy. The primary outcome measure of efficacy was the development of new or recurrent AIDS defining illness or death. Of 1156 patients, 8% developed an AIDS defining illness or died after a median follow-up of 38 weeks; 6% in the treatment arm (lamivudine plus zidovudine (or stavudine) plus indinavir) compared 11% of the comparator arm (lamivudine plus zidovudine (or stavudine)) (p=0.001). Reductions in HIV-1 RNA concentrations were

significantly lower in the treatment arm compared to the comparator arm (2.1 log_{10} vs 1.0 $log_{10,}$ p=0.007) (Hammer et al., 1997). Mortality and slowed HIV disease progression soon became the benchmark of HIV treatment thus termed as 'highly active antiretroviral therapy'. However, early antiretroviral drug formulations required high dosages, in some instances up to 22 pills per day, for optimal treatment. The high pill burden accompanied with profound drug interactions with the ARVs induced severe adverse events. Adverse events in people receiving HAART soon became apparent and were associated with poor adherence rates, treatment limiting toxicities and subsequent virological failure (Molaghan, 1997, SK, 1997). An early HAART study that included 143 HIV infected patients observed a viral load reduction to <500 copies/mL at 6 months in less than half of the patients (47%) (SK, 1997). The disappointing study results was attributed to poor HAART adherence and an associated 15-fold increased risk of virological treatment failure (Max and Sherer, 2000). Innovations in drug formulation have since been made available which have improved the efficacy of antiretroviral drugs. An example of this was Atripla® the first single antiretroviral pill containing efavirenz, emtricitabine, and tenofovir (Julg and Bogner, 2008). Today, there are more than 25 antiretroviral agents and six classes that target the different stages of the viral life cycle as follows (BHIVA et al., 2014, HHS, 2015):

- Nucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Fusion inhibitors
- Integrase inhibitors
- Chemokine receptor 5 (CCR5) antagonists

Despite the effectiveness of HAART, now referred to as combination antiretroviral therapy (cART), it is not curative. The establishment of HIV reservoirs very early on in infection is thought to prevent sterilising immunity thereby propagating HIV persistence (Pierson et al., 2000). The primary aims of cART therefore are to: achieve and maintain full HIV viral suppression; immunological restoration and/or preservation; and reduce HIV associated morbidity and mortality (BHIVA et al., 2014, HHS, 2015). Furthermore, the use of cART reduces the risk of HIV transmission associated with a high viral load (Quinn et al., 2000, Cohen et al., 2011). Full HIV viral load suppression in the early cART era was aimed at <400 copies/mL (Max and Sherer, 2000). In recent years, an undetectable HIV viral load is considered at <50 copies/mL (BHIVA et al., 2014, HHS, 2015). There are new ultrasensitive assays that can quantify HIV RNA levels as low as 1 copy/mL (Williams et al., 2014).

Over the last decade, the choice and timing of cART initiation has been much debated. Immunological status, HIV viral load, stage of HIV infection, HIV related and non-related co-morbidities, viral co-infections and existing malignancies are some of the factors considered when initiating cART. Some researchers have argued that starting cART very early on in infection would reduce the size of the HIV reservoir and reduce the initial viral 'set point' thus improve the clinical disease course (Wasserheit, 1992, Henrard et al., 1995). Although, initiating cART during primary HIV infection has cost implications and there is the added risk of treatment limiting toxicities with chronic ART use. Majority of clinical guidelines have made recommendations of cART initiation based on immunological status (CD4 T cell count), presence of an AIDS defining illness, pregnancy, high HIV viral load (> 100,000 copies/mL), HIV-

related illnesses (e.g. kidney disease, liver disease), co-infections, drug resistance profiling and cost (Churchill et al., 2015, HHS, 2015).

Initiating cART guided by CD4 T cell count varies between guidelines. Early guidelines recommended starting cART when CD4 T cell counts were < 200 cell/mm^3. This recommendation was based on early clinical trials (Hammer et al., 1996, Hammer et al., 1997, Hogg et al., 2001, Palella et al., 2003). Furthermore, low CD4 T cell counts < 200 cells/mm^3 was associated with a high risk of opportunistic infections, AIDS defining illnesses, non-AIDS morbidity and death (Hammer et al., 1997, Mocroft et al., 1998, HTCG, 1999, Hogg et al., 2001, Palella et al., 2003, Baker et al., 2008, When To Start et al., 2009, Zolopa et al., 2009, HHS, 2010, Nelson et al., 2011). The Strategies for Management of Antiretroviral Therapy (SMART) trial observed that initiating cART when CD4 T cell counts were <250 cells/μL was associated with a three times higher rate of AIDS or death compared to a CD4 T cell count > 350 cells/μL (SMARTStudyGroup et al., 2008b, When To Start et al., 2009, Cohen et al., 2011). More recent recommendations consider starting cART at CD4 T cell counts between 350 and 500 cell/mm^3 (WHO, 2013, BHIVA et al., 2014, HHS, 2015) or any count even if > 500 cells/mm^3 (Hoen et al., 2014, INSIGHTStartStudyGroup et al., 2015, Tabernilla and Poveda, 2015). The most recent British HIV Association guidelines (2015) recommend initiating cART immediately irrespective of CD4 T cell count for primary HIV infected individuals and within two weeks for those that present with advanced HIV disease and CD4 T cell count <200 cell/mm^3 .

Data for initiating cART at CD4 T cell counts between 350 and 500 cell/mm^3 showed reduced HIV disease progression although the effect on mortality was conflicting. Evidence for initiating cART at CD4 T cell counts >500 cells/mm^3 was less conclusive though there was some benefit in the prevention of HIV transmission by fully suppressing the viral load (HHS, 2015). **Table 1** summarises the studies that support initiation of cART when CD4 T cell counts between 350 and 500 cell/mm^3 and > 500 cells/mm^3. There are also longevity benefits with early cART initiation. An HIV individual diagnosed at 35 years of age and starting cART at CD4 T cell count < 100 cell/mm^3 is predicted to live to 62 years of age while starting at CD4 T cell count > 200 cells/mm^3 is thought to extend life expectancy by 10 years to 72 years of age (Antiretroviral Therapy Cohort, 2008, Justice, 2010).

Table 1: Risk of AIDS or Mortality for HIV-1 Infected Patients maintained on Combination Antiretroviral Therapy Stratified by CD4 T Cell Count at cART Initiation

Study	N	CD4 Count at cART Initiation (cells/mm^3)	Risk of Mortality** HR (95 CI)	Reference
ART-CC	24,444	51 - 150 351-450	2·24 (1·72–2·92) Ref	(When To Start et al., 2009)
ART-CC	24,444	251 to 350 351 to 450	1·13 (0·80–1·60) Ref	(When To Start et al., 2009)
NA-ACCORD	8,362	<350 351 – 500	RR (95 CI): 1.69 (1.26–2.26)* Ref	(Kitahata et al., 2009)
NA-ACCORD	9,155	< 500 >500	1.94 (1.37–2.79) Ref	(Kitahata et al., 2009)
HIV-CAUSAL	8,392	<350 351 – 500	1.38 (1.23–1.56) Ref	(Collaboration et al., 2011)
CASCADE	5,527	200 – 349 350 – 499 500 - 799	0.71 (0.44-1.15 0.51 (0.33-0.80 1.02 (0.49-2.12	(CASCADE, 2011)
SMART	477	< 250 >350	3.5 (1.3-9.6)* Ref	(SMARTStudyGroup et al., 2008a)
START	4,685	Immediate initiation irrespective of CD4 T cell count Deferred initiation to <350	0.58 (0.28-1.17) Ref	(INSIGHTStartStudyGroup et al., 2015)
HPTN 052	1,763	<250 250 - 550	Ref 0.73 (0.52–1.03)*‡	(Grinsztejn et al., 2014)
CIPRA HT-001	816	<200 200 - 350	4.0 (1.6-9.8) Ref	(Severe et al., 2010)

Key: ART Cohort Collaboration (ART-CC); HR, Hazard Ratio; RR, Risk Ratio; 95 (CI), 95% Confidence Interval; Ref, Reference
*Risk of AIDS & Mortality; ** P <0.05; ‡P=0.074

Recommendations on the choice of cART regimen also varied between guidelines and were largely driven by clinical efficacy and cost-effectiveness studies. In the UK, the current guidelines recommend treatment for therapy naïve HIV positive individuals two NRTI, tenofovir plus emtricitabine or, abacavir plus lamivudine as an alternative and a third agent (Churchill et al., 2015). The choice of third agent should include first line either: a protease inhibitor (atazanavir or darunavir) with ritonavir as a pharmacokinetic enhancer (PI/r); or NNRTI (rilpivirine); or INI (dolutegravir, raltegravir or elvitegravir with cobicistat pharmacokinetic enhancer). Efavirenz, an NNRTI is reserved as an alternative third agent. The USA guideline recommendations are similar with the exception of the choice of PI/r which excludes ritonavir boosted atazanavir due to the high rate treatment limiting toxicities observed in clinical trials (Lennox et al., 2014, HHS, 2015). Efavirenz is also excluded from the guidelines due to central nervous system related toxicities and possible association with suicide (Mollan et al., 2014, HHS, 2015).

INI-based regimens are considered to have high virological efficacy, fewer drug interactions and much improved safety profile compared to other ARVs albeit with a low genetic barrier to resistance (Blanco et al., 2011, Walmsley et al., 2013, Molina et al., 2015). Where adherence is of concern, PI/r-based regimens are much preferred due to the high genetic barrier to resistance (Lathouwers et al., 2011, Soriano et al., 2011, HHS, 2015). However, recent data demonstrates dolutegravir having a high genetic barrier to resistance (Llibre et al., 2015).

Prescribing patterns in the UK have changed over the years. In the late 1990s majority of patients were initiated on protease inhibitor containing cART compared to NNRTI containing cART. One observational cohort study with 14,252 patients demonstrated 2% vs 19% respectively initiated NNRTI vs PI containing cART in 1996. This dramatically changed in the early to mid-2000s where 75% initiated NNRTI containing cART vs 14-18% PI containing cART (Easterbrook et al., 2008). Even with effective cART treatment that resulted in immune restoration and fully suppressed HIV viral load, the HIV population are experiencing significantly increased co-morbidities. This is thought to be as a result of: the extended life expectancy with ART use; an ageing HIV population; long-term adverse events with antiretroviral use; direct HIV viral effect; and chronic inflammatory responses driven by chronic HIV infection (Gazzola, 2010, Baranoski et al., 2014, Crawford et al., 2014, Lorenc et al., 2014, Warriner et al., 2014).

1.3. HIV and Co-morbidities

Effective antiretroviral therapy has vastly improved the survival of people living with HIV. Longevity and the ageing HIV population has increased the risk of developing non-HIV related comorbidities including renal disease, liver disease, cardiovascular disease, chronic lung disease, diabetes, neurologic conditions (e.g. HIV-associated dementia) and non-AIDS related malignancies (Friis-Moller et al., 2003b, Grinspoon, 2009, Falade-Nwulia and Thio, 2011, Aberg, 2012, Medapalli et al., 2012, Manji et al., 2013, Rodriguez-Penney et al., 2013). This section will briefly discuss the common co-morbidities observed in the HIV infected population.

Aging & HIV

In the UK and USA about one third of all HIV infected patients are over the age of 50 (CDC, 2011, HPA, 2014). The chronic inflammatory responses and immunosenescence during HIV infection is thought to be the cause of these combined HIV and age related co-morbidities (Aberg, 2012). Despite the effective HIV suppression and somewhat improved immunological function with antiretroviral therapy, evidence of persistent inflammation and lower CD4 T cell counts increase the risk of non-AIDS comorbidities (Deeks and Phillips, 2009). Aside from inflammation, HIV infected individuals differ greatly to HIV uninfected patients in lifestyle and socioeconomic status that may further increase the risk of developing comorbidities. **Figure 3** shows a conceptual model of aging in people living with HIV. Among HIV infected individuals, smoking, alcohol and drug use is highly prevalent (Justice, 2010). It is estimated that 40 to 75% of HIV infected individuals smoke cigarettes (Pacek and Cioe, 2015). Cigarette smoking has been known to increase the risk of AIDS and non-AIDS related diseases (Calvo-Sanchez et al., 2013, Helleberg et al., 2013, Shirley et al.,

2013, Helleberg et al., 2015). Chronic obstructive pulmonary disease, lung cancer, atherosclerotic disease, decreased bone mineral density, human papillomavirus (HPV) and related cancers are but some of the comorbidities associated with smoking in HIV infected individuals (Castellsague and Munoz, 2003, Minkoff et al., 2004, Shirley et al., 2013).

Figure 3: ***Ageing & HIV***

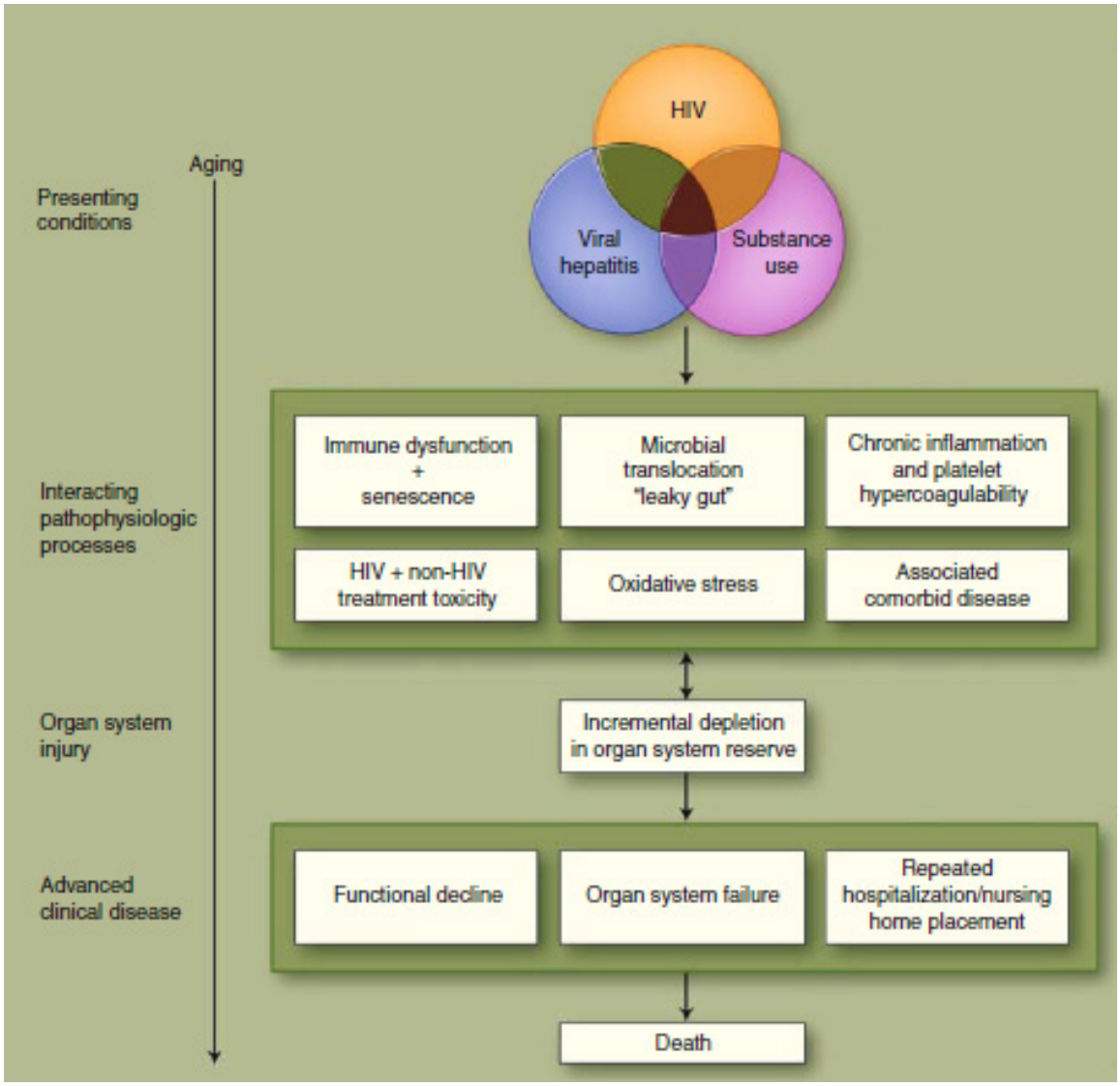


Figure 3 Adapted from *"HIV and Aging: Time for a New Paradigm"* (Justice, 2010). Conceptual model of aging with HIV infection. Viral hepatitis and continual substance use (e.g. smoking, alcohol, drug use, etc) aggravate immune dysfunction and chronic inflammation thereby worsening co-morbid disease and both HIV and non-HIV treatment toxicities.

Cardiovascular disease & HIV

Aside from inflammatory and lifestyle factors, metabolic complications such as cardiovascular disease and diabetes are common among the aging HIV infected individuals (Falutz, 2011, Petoumenos and Worm, 2011). Lipid changes and atherosclerotic changes associated with low levels of high-density lipoprotein and high levels of low-density lipoprotein cholesterol are predominant among HIV individuals. This is brought about by direct HIV effects, ageing and metabolic complications associated with continuous antiretroviral therapy use (Kaplan et al., 2011) (Lagathu et al., 2004, Giralt et al., 2010, Falutz, 2011). Epidemiology studies have reported almost 2 fold increased risk of cardiovascular disease among HIV infected individuals on cART compared with HIV uninfected patients (Islam et al., 2012, Martin-Iguacel et al., 2015). Arterial inflammation, coronary artery plaque, carotid artery intima-media thickness and HIV associated lipodystrophy with antiretroviral therapy have been observed in HIV infected patients (Abd-Elmoniem et al., 2014, Freitas et al., 2014, Post et al., 2014, Samuel et al., 2014).

The D:A:D study was the first observational cohort study, that included 49,734 HIV infected patients, which showed an association of cART treatment and cardiovascular disease (Friis-Moller et al., 2003a, Martin-Iguacel et al., 2015). The study reported an increased relative risk (26%) of acute myocardial infarctions from prolonged use of cART (4 to 6 years). Antiretroviral therapy induced lipodystrophy is also known to contribute to the development of atherosclerotic lesions (Guaraldi et al., 2010). Lipodystrophy occurs more commonly with protease inhibitors and thymidine nucleoside reverse transcriptase inhibitors compared to NNRTI and other classes of antiretroviral

therapy (Guaraldi et al., 2014). There are also differences in dyslipidemic, atherogenic and prothrombotic effects between individual antiretroviral drugs within the same class (Martin-Iguacel et al., 2015). An example of this was demonstrated in the SENSE study where efavirenz use was associated with greater lipid elevations compared to Etravirine (Fatkenheuer et al., 2012, Guaraldi et al., 2014). At the end of the 48 week study, compared to etravirine patients on efavirenz demonstrated greater change in HDL (+0.15 mmol/L, p=0.004), LDL (+0.35 mmol/L, p=0.005), total cholesterol (+0.61 mmol/L, p<0.0001) and triglycerides (+0.33 mmol/L, p=0.03). In another study, total cholesterol and triglycerides were significantly raised with efavirenz compared with rilpivirine (Wilkin et al., 2012). By the end of the 192 week study, the mean change in lipids from baseline for rilpivirine vs efavirenz respectively was: total cholesterol (-17 (35) vs -41 mg/dl, p<0.001); LDL (-10 vs -22 mg/dl, p<0.01); HDL (+5 vs +11 mg/dl, p<0.001). In the D:A:D observational cohort study the risk of myocardial infarction (MI) was lower in those on NNRTI but higher with PI containing cART (D.A.D.StudyGroup et al., 2007). An overall of 345 fatal/non-fatal myocardial infarctions were observed; 90.4% and 60.9% of the events respectively occurred in patients that had a median of 3.7 years of PI exposure versus 2.1 years of NNRTI exposure.

The D.A.D study group also found an almost two fold increase in risk of developing a myocardial infarction with abacavir exposure (RR 1.89) (D.A.D.StudyGroup et al., 2008). The association of abacavir exposure and MI remained even after adjusting for renal impairment (Post and Campbell, 2008, Martin-Iguacel et al., 2015). Although, there were criticisms that the D.A.D study did not address underlying cardiovascular risk, especially in those patients at high risk of CVD, as a confounding factor. A recent update analysis

within the D.A.D cohort observed a 98% increase in MI rate with current abacavir use and a rate ratio of 1.98 adjusted for CVD risk factors including renal, dylipidaemia and hypertension. The associated CVD risk with abacavir use remained when analyses were split before and after 2008 when the first study was published (Sabin, 2014).

Liver disease & HIV

Liver disease is one of the major causes of death which accounts for 14 – 18% of all deaths among HIV infected individuals. In the post-cART era, liver disease is largely due to hepatitis B / C co-infection and medication related toxicity (Antiretroviral Therapy Cohort, 2010, Price and Thio, 2010). An estimated 30% of HIV infected individuals in the USA and Europe are co-infected with hepatitis C. Worldwide 10% of all people living with HIV are infected with hepatitis B. HIV infected individuals are 3 to 6 times more likely to develop chronic hepatitis B after acute exposure compared to HIV uninfected individuals (Bodsworth et al., 1991, Price and Thio, 2010). An accompanying low CD4 T cell count (<200 cells/mm^3) further compromises immunity to HBV among HIV infected patients (Kim et al., 2008). ART-associated hepatotoxicity is one of the most common serious adverse effects with an approximate 10% incidence rate (Sulkowski et al., 2000, Puoti et al., 2009, Price and Thio, 2010). Different mechanisms known to induce ART-associated liver toxicity include hypersensitivity reactions, mitochondrial toxicity, direct drug toxicity or drug metabolism and immune reconstitution inflammatory syndrome (IRIS) (Anderson et al., 2010, Price and Thio, 2010). Furthermore, immune restoration in viral co-infected HIV infected patients compromises the liver causing cirrhosis and hepatic dysfunction (Zylberberg et al., 1998, Drake et al., 2004, Price and Thio, 2010).

Aside from ART use, alcohol, older age, female gender and concomitant anti-tuberculosis medications are all factors associated with ART-associated liver damage (Hoffmann et al., 2007, Soriano et al., 2008, Puoti et al., 2009, Price and Thio, 2010). Drug interactions and co-medication are other additional factors that may increase risk of ART related liver toxicity. For example, HIV/HCV co-infected individuals receiving HCV treatment with ribavirin and pegylated interferon have demonstrated an increased risk of mitochondrial toxicity and anaemia with zidovudine containing cART (Soriano, 2006, Price and Thio, 2010). Another example, is the higher incidence of liver steatosis observed when stavudine is co-medicated with HCV treatment (McGovern et al., 2006).

Bone disease & HIV

Low bone mineral density is expected among the ageing population. HIV infection and the chronic use of antiretroviral drugs are independent risk factors for the development of osteoporosis (Duvivier et al., 2009, McComsey et al., 2011, Guaraldi et al., 2014). The inflammatory responses associated with HIV infection are thought to cause an imbalance in bone turnover, osteoporosis and bone loss (Ofotokun and Weitzmann, 2011). Reduced vitamin D levels are associated with certain antiretroviral drugs, such as efavirenz containing cART, and renal insufficiency (Dao et al., 2011, Viard et al., 2011, Childs et al., 2012). In the EuroSIDA cohort, vitamin D deficiency was observed in approximately 83% of HIV infected patients on ART (n=1985) (Viard et al., 2011).

Neurological complications of HIV

Neurological damage that is associated with cognitive impairment has become increasingly common in the ageing HIV infected population (Becker et al., 2004, Kissel et al., 2005, Sacktor et al., 2007). In the CHARTER study, an estimated 40% of HIV infected patients were diagnosed with neurocognitive impairment (Heaton et al., 2010). Neuroimaging studies in HIV infected individuals have shown changes to both grey and white matter that demonstrates an increased risk of HIV-associated neurocognitive disorders including dementia (Valcour et al., 2004, Larussa et al., 2006). Other factors that may potentiate neurological damage include: substance misuse; central nervous system (CNS) ART related toxicities; ageing; syphilis; and HCV co-infection (Guaraldi et al., 2014).

HIV & the Kidney

Renal disease is an important comorbid condition in HIV infection. Abnormal renal function of any cause is estimated in 30% of all HIV infected individuals (Gupta et al., 2005). The aetiology of kidney disease in HIV infected individuals has been well studied. Direct HIV and immunological effects, both immunodeficiency and chronic inflammatory effects; have been implicated in the development of kidney disease in HIV infected individuals. HIV infection of the renal epithelial cells, immune complex deposits in the renal tissue and thrombotic microangiopathy induced by HIV are other known causes of HIV-associated kidney disease (Kimmel et al., 1993a, Ahmed et al., 2002, Ross et al., 2006). Although, the spectrum of kidney diseases differs in HIV infected individuals with advanced immunodeficiency compared to those with well controlled HIV disease. **Table 2** summarises kidney diseases in HIV infection.

Table 2: Kidney Diseases in HIV Infection

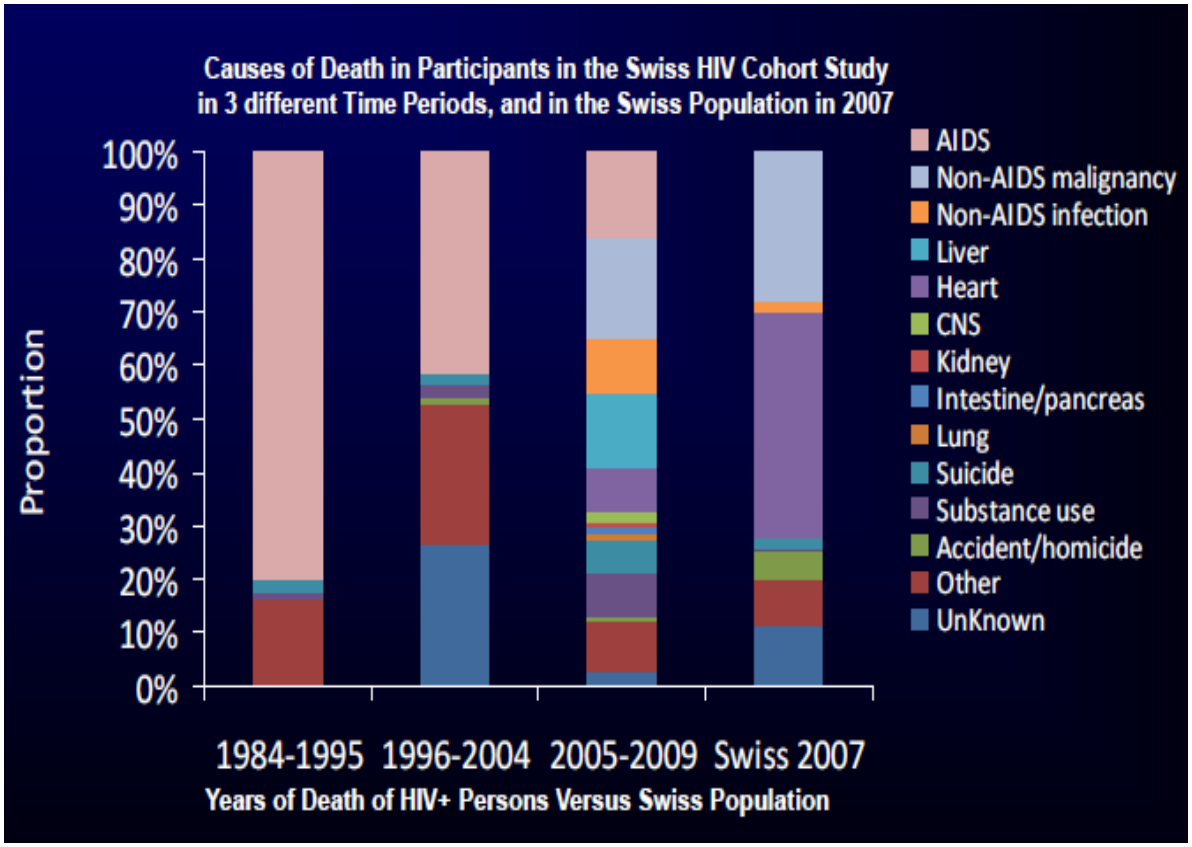
HIV Related	Non HIV Related
HIV-associated nephropathy	Membranoproliferative GN
HIV-related immune complex disease immune complex–mediated GN IgA nephritis mixed sclerotic/inflammatory lupus-like disease	Cryoglobulinaemic GN
Thrombotic microangiopathy	Post-infectious GN Classic FSGS Diabetic nephropathy Amyloidosis Membranous glomerulopathy Minimal change disease IgA nephropathy ART related toxicity Renal tubular dysfunction Acute tubular injury Tubulointerstitial nephritis Interstitial fibrosis and tubular atrophy

Key: GN – glomerular nephropathy; IgA - Immunoglobulin A; FSGS - Focal segmental glomerulosclerosis; ART – Antiretroviral drug therapy

In the pre-HAART era, HIV associated nephropathy was the most common form of kidney disease among HIV infected patients. The incidence of HIVAN and other kidney diseases associated with advanced HIV disease are therefore expected to decline with HAART use (Atta et al., 2008, Post et al., 2008, Wyatt et al., 2008b, Post and Holt, 2009). However, no reduction but instead a plateau in the occurrence of HIVAN has been observed in the post-HAART era. An example of this was observed in the USA where in 1990 there were 150 cases of HIVAN compared to 2700 cases at the end of 2005 (Schwartz et al., 2005, Wyatt et al., 2008a). The increase in cases was thought to be due to an improvement in HIV survival with antiretroviral use. Furthermore, a decline in kidney disease as a cause of death in HIV infected individuals has also been observed, (see **Figure 4**) (Weber et al., 2013).

With the introduction of HAART, other factors associated with an ageing population and chronic multi-medication use has contributed to the development of kidney disease in the HIV population. Other factors associated with kidney disease in HIV infection include: HIV as an independent risk factor; black ethnicity; diabetes; hypertension; HIV viraemia; drug related renal toxicity; and age (Madeddu et al., 2006, Winston et al., 2008, Bruggeman et al., 2009, Naftalin et al., 2011).

Figure 4: Causes of Death in the Swiss HIV Cohort Study



Graph adapted from Jones R and Post FA presentation at BHIVA Autumn Conference (2011) and Ruppik et al CROI Conference. Abstract 789 (2011)

Acute and chronic renal failure is highly prevalent in the HIV population (Wyatt et al., 2006, Mocroft et al., 2007, Wyatt et al., 2007, Campbell et al., 2009). In ARF specifically, exposure to nephrotoxic agents including ARVs and in some instances medication used to treat opportunistic infections have been implicated (Gupta et al., 2005). Sepsis, hepatitis B/C co-infection, high viral load, immunodeficiency and pre-existing renal impairment are additional factors that predispose HIV infected patients to ARF (Ibrahim et al., 2010, Maggi et al., 2012a). The incidence rate of ARF has been estimated between 2.7 to 5.9 episodes per 100 person years (Franceschini et al., 2005, Roe et al., 2008). In

the general population, the incidence of ARF ranges from 0.9 to 20% in developed countries (Lameire et al., 2008). Antiretroviral drug induced toxicity can result in rapid decline of renal function. Exposure to indinavir and tenofovir respectively have demonstrated a 4.6 and 3.7 fold rapid renal function decline in HIV infected patients with existing renal impairment (Campbell et al., 2009).

ART induced toxicity has several mechanisms including: renal obstruction or crysllurìa; acute interstitial nephritis; and renal tubular disease (Fine et al., 2008, Hamzah et al., 2015b). **Table 3** summarises the kidney effects of currently available antiretroviral drugs. Renal tubular disease is characterised by three distinctive patterns; acute tubular injury, tubulointerstitial nephritis and interstitial fibrosis and tubular atrophy. A recent renal biopsy study identified 22.6% (n=60) of HIV infected individuals diagnosed with renal tubular disease. Acute tubular injury was more common and associated with cART exposure especially tenofovir and atazanavir (Hamzah et al., 2015b). In the same study, no evidence of tubulointerstitial nephritis, interstitial fibrosis and tubular atrophy was associated with ART exposure – tenofovir, atazanavir or lopinavir.

Tenofovir is the most common antiretroviral drug implicated in nephrotoxicity (Fine et al., 2008). Subclinical evidence of proximal tubular dysfunction has been observed in 25 to 80% of HIV infected patients taking tenofovir disoproxil fumarate formulation (Franceschini et al., 2005, Ray et al., 2006, Nelson et al., 2007, Hall et al., 2009, Choi et al., 2010, Ando et al., 2011, Maggi et al., 2012b, Wyatt, 2014, Hamzah et al., 2015b). The newer formulation, tenofovir alafenamide yields lower plasma tenofovir concentrations and consequently demonstrated improvements in biomarkers of renal tubular function compared to tenofovir DF formulation (Sax et al., 2015).

Table 3: The Kidney Effects of Antiretroviral Drug Therapy & Antiretroviral Dose Adjustment for Renal Impairment

ANTIRETROVIRAL DRUG	KIDNEY ABNORMAL EFFECTS	ANTIRETROVIRAL RENAL DOSE ADJUSTMENT
Nucloside/nucleotide reverse transcriptase inhibitors		
Abacavir	Acute interstitial nephritis	No dosage adjustment necessary
	Fanconi syndrome	
Didanosine	Fanconi syndrome	Renal dose adjustment necessary
	Acute kidney injury	
	Nephrogenic diabetes insipidus	
Emtracitabine	No kidney effects reported	Renal dose adjustment necessary
Lamivudine	Renal tubular acidosis	Renal dose adjustment necessary
	Hypophosphatemia	
Stavudine	Renal tubular acidosis	Renal dose adjustment necessary
	Hypophosphatemia	
Tenofovir Disoproxil Fumarate	Proximal tubular dysfunction	Renal dose adjustment necessary
	Fanconi syndrome	
	Acute kidney injury	
	Nephrogenic diabetes insipidus	
	Hypophosphatemia	
Tenofovir alafenamide fumarate	No kidney effects reported	No dosage adjustment necessary
Zidovudine	No kidney effects reported	Renal dose adjustment necessary
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine	No kidney effects reported	No dosage adjustment necessary
Delavirdine	No kidney effects reported	No dosage adjustment necessary
Efavirenz	Nephrolithiasis	No dosage adjustment necessary
Rilpivirine	Reduced creatinine excretion; no renal toxicity effects	No dosage adjustment necessary
Protease inhibitors		
Amprenavir	No kidney effects reported	No dosage adjustment necessary
Atazanavir	Acute interstitial nephritis	No dosage adjustment necessary
	Nephrolithiasis	No dosage adjustment necessary
Darunavir	Nephrolithiasis	No dosage adjustment necessary
Fosamprenavir	None reported	No dosage adjustment necessary
Indinavir	Acute kidney injury (acute interstitial nephritis)	No dosage adjustment necessary
	Chronic kidney disease (acute interstitial nephritis)	No dosage adjustment necessary
	Nephrolithiasis	No dosage adjustment necessary
	Intratubular drug precipitation	No dosage adjustment necessary
	Papillary necrosis	No dosage adjustment necessary
	Hypertension	No dosage adjustment necessary
	Renal atrophy	No dosage adjustment necessary
Lopinavir	Nephrolithiasis	No dosage adjustment necessary
Nelfinavir	Nephrolithiasis	No dosage adjustment necessary
Ritonavir (treatment doses)	Acute kidney injury	No dosage adjustment necessary
Saquinavir	Acute kidney injury in association with ritonavir	No dosage adjustment necessary
Tipranavir	No kidney effects reported	No dosage adjustment necessary
Fusion inhibitors		
Enfuvirtide	Membranoproliferative glomerulonephritis	No dosage adjustment necessary
CCR5 antagonist		
Maraviroc	No kidney effects reported	Renal dose adjustment necessary
Integrase inhibitor		
Raltegravir	No kidney effects reported	No dosage adjustment necessary
Dolutegravir	Reduced creatinine excretion; no renal toxicity effects	No dosage adjustment necessary
Elvitegravir with cobicistat	Reduced creatinine excretion; no renal toxicity effects	No dosage adjustment necessary
Pharmacokinetic enhancer		
Cobicistat	Reduced creatinine excretion; no renal toxicity effects	No dosage adjustment necessary

References: (Duong et al., 1996, Chugh et al., 1997, Daudon et al., 1997, Kopp et al., 1997, Rich et al., 1997, Tashima et al., 1997, Witzke et al., 1997, Bochet et al., 1998, Guardiola et al., 1998, Martinez et al., 1998, Benveniste et al., 1999, Cattelan et al., 2000, Gagnon et al., 2000, Jaradat et al., 2000, Krishnan et al., 2000, Cattelan et al., 2001, Dieleman et al., 2001, Morris et al., 2001, Salahuddin et al., 2001, van Rossum et al., 2001, Coca and Perazella, 2002, Engeler et al., 2002, Kopp et al., 2002, Verhelst et al., 2002, Creput et al., 2003, Karras et al., 2003, Lalezari et al., 2003, Rollot et al., 2003, Schaaf et al., 2003, Brewster and Perazella, 2004, Izzedine et al., 2004, James et al., 2004, Peyriere et al., 2004, Rifkin and Perazella, 2004, Izzedine et al., 2005, Ahmad, 2006, Chang and Pella, 2006, Pacanowski et al., 2006, Wirth et al., 2006, Zimmermann et al., 2006, Chan-Tack et al., 2007, Couzigou et al., 2007, Izzedine et al., 2007, Fine et al., 2008, Gupta, 2008, Nakatani-Freshwater and Taft, 2008, Izzedine et al., 2009a, Kalyesubula and Perazella, 2011, Gupta, 2012, Ramanathan, 2013, Izzedine et al., 2014, HHS, 2015, eMC, n.d, PhP, n.d)

Several factors are known to influence the progression of kidney disease in HIV infected patients managed on cART. Chronic kidney disease is characterised by sustained proteinuria or albuminuria and estimated glomerular filtration rate < 60 ml/min/1.73 m^2 for more than 3 months (Campbell et al., 2009, Levey et al., 2009). The prevalence of CKD defined by eGFR < 60ml/min/1.73 m^2 is estimated at 2.4 to 23.7% (Gupta et al., 2004, Gupta et al., 2005, Cheung et al., 2007, Wyatt et al., 2007, Fernando et al., 2008, Campbell et al., 2009, Maggi et al., 2012a). Proteinuria in HIV infected individuals is quite frequent with an estimated 7.2 to 48.5% of patients presenting on urinary screening during routine clinical care (Szczech et al., 2002, Gardner et al., 2003, Gupta et al., 2004, Szczech et al., 2004, Cheung et al., 2007, Wyatt et al., 2007, Fulop et al., 2010, Estrella et al., 2011, Yanagisawa et al., 2011, Naicker et al., 2015). A further estimated 8.7 to 17.8% of HIV infected patients present with albuminuria (Szczech et al., 2007, Baekken et al., 2008, Yanagisawa et al., 2011).

Risk factors associated with developing proteinuria in HIV infected include black ethnicity, low CD4 T cell count (< 200 cells/mm^3), hepatitis C co-infection and HIV viraemia (Yanik et al., 2010, Gravemann et al., 2014). A high level of HIV viraemia accompanied with a low CD4 T cell count (< 200 cells/mm^3) are both strong and independent predictors for developing renal impairment in HIV infected patients with proteinuria (HR 3.6 and 2.3 respectively) (Szczech et al., 2002, Post and Hendry, 2008). Advanced HIV disease which can cause both viral and immunological mediated renal diseases may often be accompanied with moderate to severe proteinuria (>0.5g/day [normal value < 0.02 g/day (Viswanathan and Upadhyay, 2011)) (Post and Hendry, 2008). However, disparities among ethnic groups have been observed. A USA cohort study demonstrated severe proteinuria (>3g/day) in 45% of African Americans

(n=1499/3332) compared to 4% (n=37/927) of Caucasian HIV infected patients (Lucas et al., 2008).

The development of CKD in HIV infected patients is associated with several factors that can be HIV related and non-HIV related. These factors include ethnicity, older age, AIDS defining illnesses, higher viral load, diabetes, hypertension, hepatitis C co-infection, gender, non-AIDS malignancy, specific cART use (tenofovir, indinavir, atazanavir, lopinavir) and other co-medication (e.g. non-steroidal anti-inflammatory drugs) (Mocroft et al., 2010, Flandre et al., 2011, Ando et al., 2012, Ryom et al., 2013b). However, immune restoration and viral suppression with cART use have demonstrated reduced risk of CKD (Kalayjian et al., 2012).

Ethnicity is an important and independent risk factor for CKD. HIV infected individuals of black ethnicity have a genetic predisposition to kidney disease owing to the apolipoprotein L1 (APOL 1) and non-muscle myosin heavy chain 9 (MYH9) genes (Nunez et al., 2010, Hays et al., 2012, Estrella et al., 2013, Foster et al., 2013, Johnstone et al., 2013, Colares et al., 2014, Estrella et al., 2015, Naicker et al., 2015). APOL1 gene risk alleles G1 and G2 are strongly associated with developing several forms of kidney disease including focal segmental glomerulosclerosis (FSGS), diabetic nephropathy, hypertensive nephropathy, and HIVAN (Kao et al., 2008, Kopp et al., 2008, Winkler et al., 2010, Kopp et al., 2011, Freedman and Murea, 2012, Hays and Wyatt, 2012, Pollak et al., 2012, Foster et al., 2013). The prevalence of APOL1 gene risk alleles G1 and G2 is estimated at 35% in the African American population (Friedman et al., 2011). There is a 7 to 10 fold increased risk of developing FSGS and HIVAN in individuals homozygous for APOL1 risk alleles G1 and G2 (Genovese et al., 2010, Friedman et al., 2011, Kopp et al., 2011, Brown et al.,

2014). APOL1 gene has also demonstrated a 3 fold increased risk of developing end-stage kidney disease in HIV infected individuals (Fine et al., 2012, Kasembeli et al., 2015).

Progression to end-stage kidney disease in HIV infected individuals varies with underlying kidney disease aetiology. HIV associated nephropathy occurs more commonly in patients with advanced HIV disease. HIVAN has demonstrated a more rapid progression to ESKD compared to other forms of kidney disease in HIV infected patients. Aside from the underlying kidney disease, as previously discussed, ethnicity plays an important role in ESKD progression. In HIV infected African Americans with existing chronic kidney disease, progression to ESKD is significantly more rapid compared to their Caucasian counterparts (HR 95CI, 17.7 (2.5 – 127.0)) (Lucas et al., 2008). The overall risk of developing ESKD in HIV infected patients is almost 50 fold higher in African Americans than in Caucasian patients (Eggers and Kimmel, 2004, Lucas et al., 2008). Although the widespread use of cART has reduced the incidence of HIVAN, the overall prevalence has increased. In the UK, the overall prevalence of ESKD among HIV infected individuals has been estimated at 0.31% (Bansi et al., 2009); almost 6 fold higher than the general population (0.08% (UKRR, 2012)). In other European countries and North America respectively, the prevalence rates range from 0.36 – 0.64% (Trullas et al., 2008, Mazuecos et al., 2012, Bickel et al., 2013, Ryom et al., 2013a, Rasch et al., 2014) and 0.75 – 1.65% (Jotwani et al., 2012, Abraham et al., 2015). A further in depth discussion on the clinical epidemiology of ESKD in HIV disease is discussed in Chapter 2.

1.4. Solid Organ Transplantation in HIV Infection

End-stage kidney disease is an important co-morbidity in the HIV infected population. Conservative management and dialysis are some of the treatment modalities available to manage ESKD in HIV infected patients. Although, outcomes from a single study suggests poor patient survival rates with the use of dialysis (median 20 months) or conservative management (median 6 months) (Post and Holt, 2009) (O'Connor and Kumar, 2012).

Kidney transplantation offers an attractive treatment modality with improved morbidity, mortality and quality of life in the general population (Griva et al., 2013, Calestani et al., 2014). Use of immunosuppressant drug therapy has dramatically improved the post-transplant management of kidney transplant recipients in the general population (BTS, 2011, 3C.StudyCollaborativeGroup et al., 2014). An increased uptake of KT in the general population has been observed, (see **Figure 5 and 6**). By the end of 2013, there were 56,940 patients in the general UK population were on permanent renal replacement therapy (pRRT) and kidney transplantation was the most common choice of treatment modality (52%). The proportion of patients on haemodialysis and peritoneal dialysis respectively was 41.6% and 6.4% (UKRR, 2014). The proportion of HIV infection in those on pRRT is estimated at 0.51% in the UK (Bansi et al., 2009). Patient survival irrespective of treatment modality choice has remained stable over the years. One year prevalent survival of ESKD pRRT patients on dialysis in 1999 and 2012 respectively was 84.8% and 85.5%. However, patient survival when comparing pRRT treatment modalities was worse in those on dialysis compared to kidney transplantation. Patient survival at one year of kidney transplant recipients was 97.5% in 1999 and ranging from 96 to 99% in 2012 (UKRR, 2000, UKRR, 2014).

Figure 5: Trends in Permanent Renal Replacement Therapy in the United Kingdom

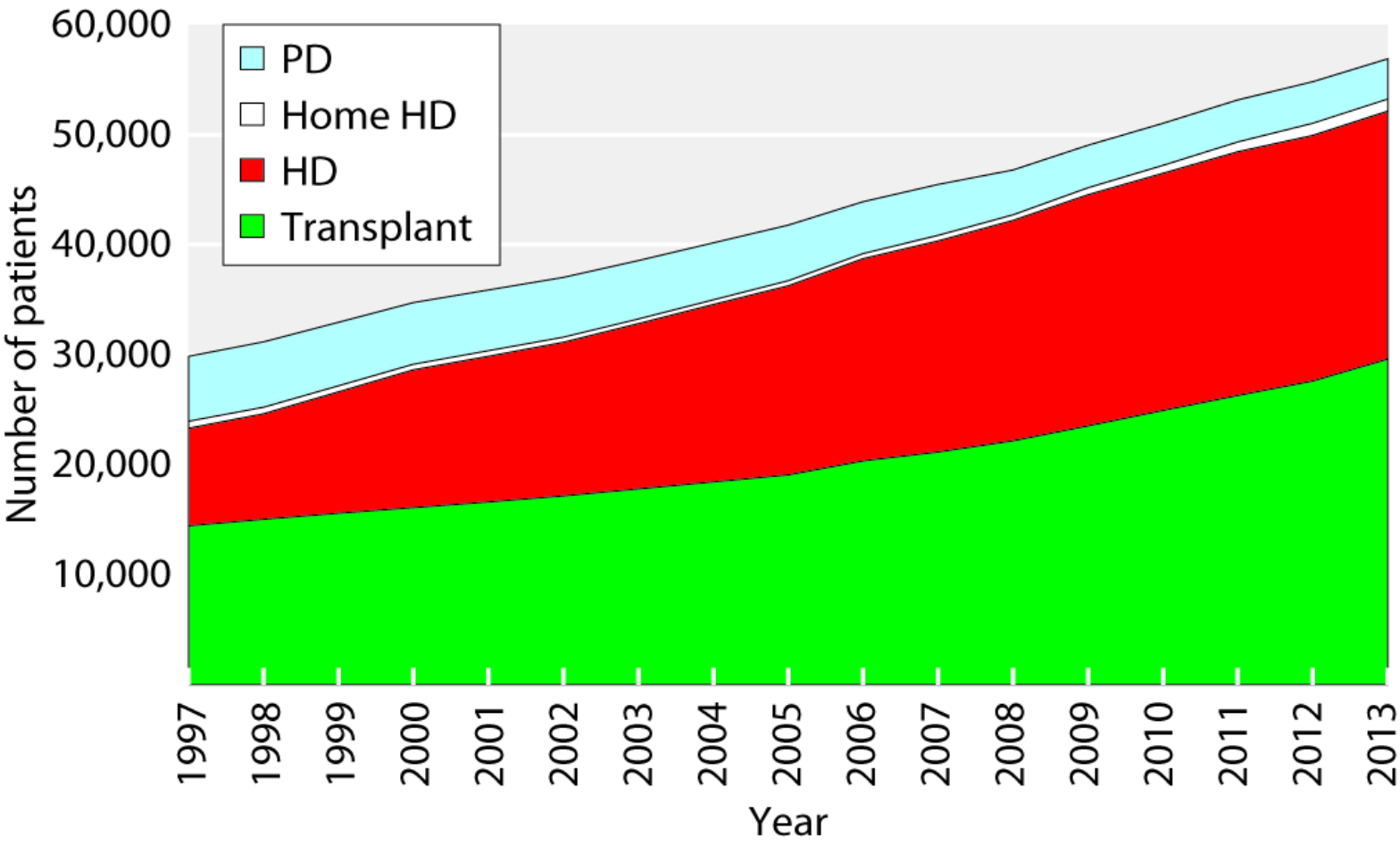
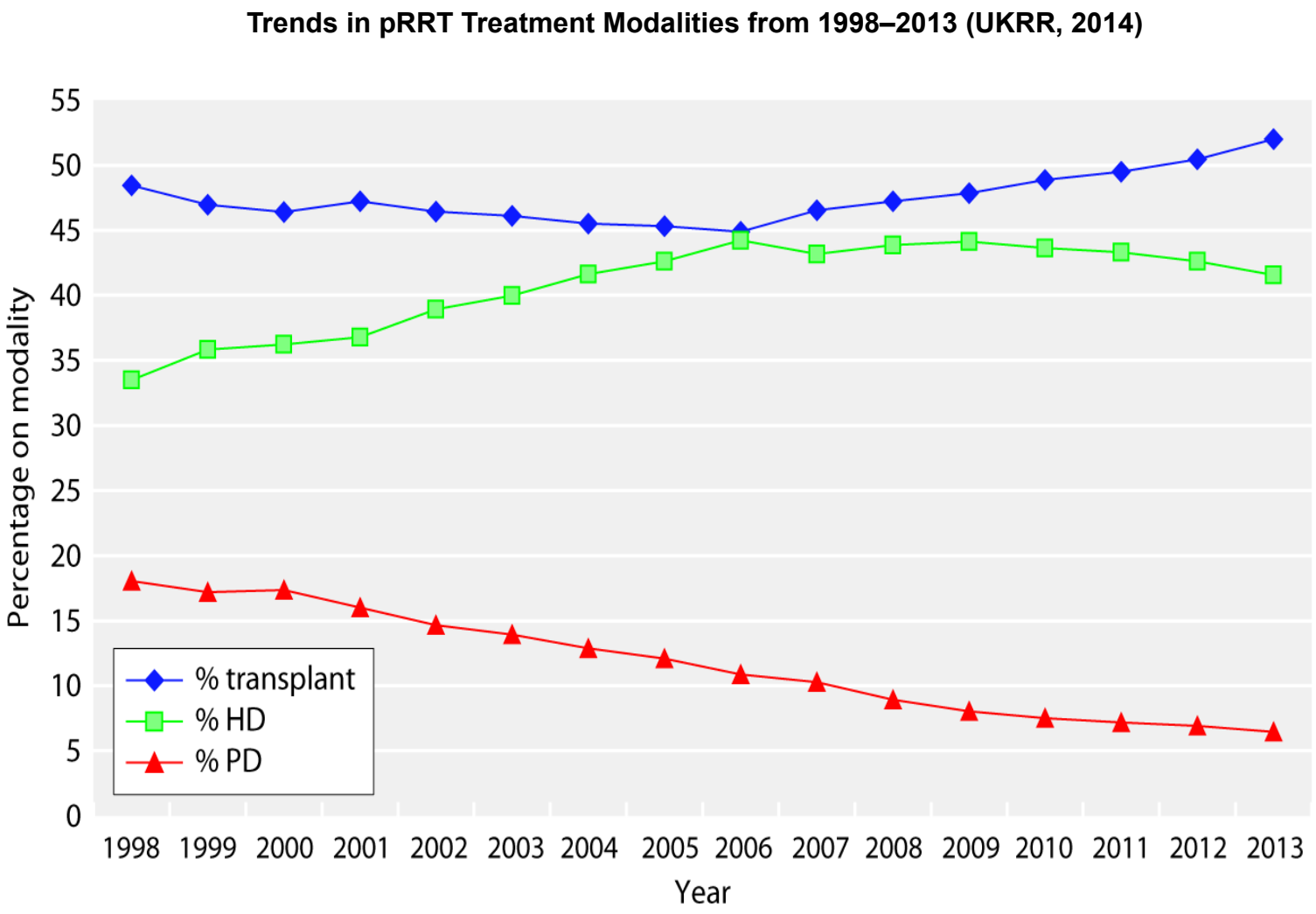


Figure 6: Trends in Permanent Replacement Therapy by Treatment Modality in the United Kingdom



Kidney transplantation in HIV infected individuals in the pre-HAART era was associated with unfavourable outcomes. These observations were owing to the poor HIV virological control and severe immunodeficiency prior to the discovery of effective antiretroviral therapy. This prompted the decision by some Transplant registries to contraindicate the use of donor organs in HIV infected candidates (Roland, 2004, Bhagani et al., 2006). There were also concerns of opportunistic infections and HIV disease progression with immunosuppressant drug use. During the pre-HAART era, kidney transplantation was mostly incidental with recipients having acquired HIV by receiving an organ from an HIV infected individual (Prompt et al., 1985, al-Sulaiman et al., 1989, Glassock et al., 1990, Lang and Niaudet, 1991, Keay et al., 1993, Schvarcz et al., 2000). This early experience of kidney transplantation was associated with a high mortality rate (46.2% at 2 years) (Trullas et al., 2011b). Better management of HIV infection with potent antiretroviral drugs paved the way for kidney transplantation as a potential option for people living with HIV. In early 2000s, a pilot study was conducted that included a highly selective group of HIV infected individuals (n=10) with fully suppressed HIV-1 RNA (< 50 copies/mL) and a CD4+ T cell count > 200 cells/mm^3 and lacking history of opportunistic infections or malignancies (Stock et al., 2003b). Patient and graft survival was 100% at 1 year albeit a high rate of allograft rejection (50%). Authors also noted profound immunosuppressant and antiretroviral drug interactions. Patients receiving protease inhibitor containing cART required ¼ of the normal dose of ciclosporin. There was no evidence of HIV disease progression. Chapter 3 contains a further in depth discussion of kidney transplantation.

1.5. HIV Kidney transplantation in the early cART era (2005 - 2009) – Literature Review

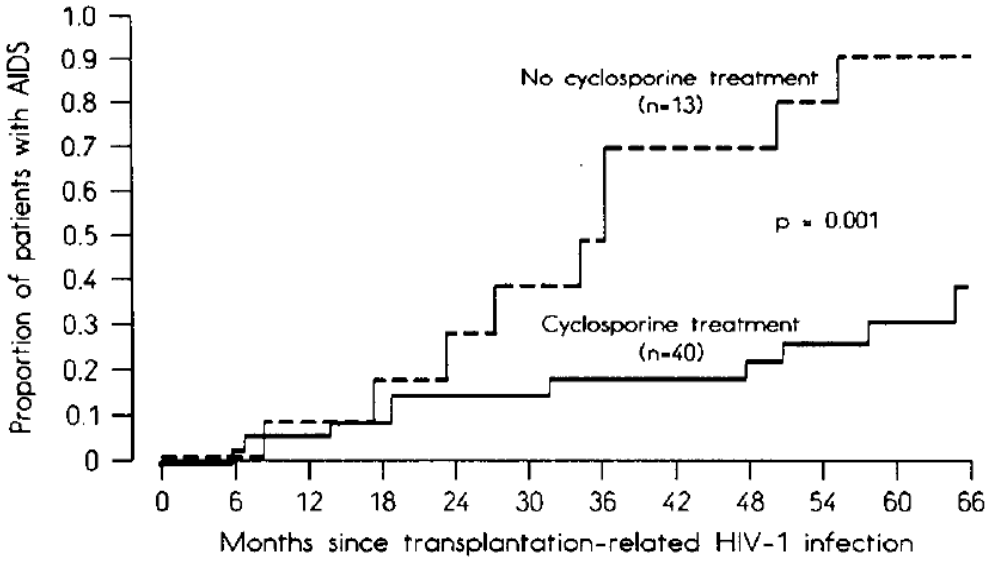
In the early 1980s, the HIV virus was discovered as the cause of Acquired Immune Deficiency Syndrome (AIDS) (Barre-Sinoussi et al., 1983, Gallo et al., 1984, Popovic et al., 1984) by which point researchers estimated between 100,000 and 300, 000 people had been infected globally (Baumann et al., 1991). At the same time, ciclosporin had been discovered as an immunosuppressive agent that would improve kidney transplantation; an area that was still in its infancy. During this period, there were the reports of transplant recipients having similar infection profiles to AIDS victims some even progressing to AIDS (Rubin et al., 1987). Of note was the profound T cell lymphopenia in both HIV infected and HIV negative immunosuppressant treated transplant recipients that resulted in severe opportunistic infections (Carbone et al., 1988).

Preventative measures to halt the spreading of HIV led to the screening of biological products, blood or donor organs. It soon became apparent that there were solid organ transplant recipients that had been infected through blood transfusions, dialysis or by receiving an organ from a HIV positive donor (Feduska et al., 1987, Kerman et al., 1987). These early reports were less focused on preventing allograft rejection with immunosuppressive agents but instead highlighted the complications that were associated with a high risk of mortality. Although, emerging data from this period demonstrated that those

with secondary HIV infections (acquired post-transplant) did better than primary HIV infections (acquired pre-transplant) in that they survived longer despite opportunistic infections and superimposed IS therapy (Ribot and Eslami, 1992). There was also some debate on whether to withdraw the immunosuppressant drugs due to their added risk of acquiring opportunistic infections in HIV infected transplant recipients (Margreiter et al., 1986a). By contrast, some case reports suggested that post-transplant rejection episodes enhanced HIV viral propagation and therefore deemed it necessary to maintain HIV/KT recipients on immunosuppressive agents (L'Age-Stehr et al., 1985, Margreiter et al., 1986b, Neumayer et al., 1986, Oliveira et al., 1986). Later, a review of 53 cases of acquired HIV-1 infection at or post-transplantation between 1985-1992, demonstrated a profound reduction in the cumulative risk of developing AIDS in patients taking ciclosporin compared to other immunosuppressive agents (31% vs 90% after 5 years, p=0.001) (see **Figure 7**) (Schwarz et al., 1993a). This is what led to researchers to suspect if ciclosporin had anti-HIV properties as HIV targeted activated CD4 cells and ciclosporin impedes T cell activation (Margreiter et al., 1986a).

Figure 7: Cumulative Incidence of AIDS in Transplant Recipients (1985-1992)

A comparison of ciclosporin vs other immunosuppressant drug treatment (Schwarz et al., 1993b)



Life table analysis of 53 primary and secondary HIV infected transplant recipients. Comparison by log-rank analysis.

There are few reports on kidney transplantation in primary HIV infected patients which are summarised in **Table 4**. Outcomes demonstrated good patient and graft survival within the first 12 months; and in one case the patient had a remarkable survival of 9 years (Ahuja et al., 1997). Early allograft rejection was noted in all but one case in whom ciclosporin monotherapy was used for a simultaneous pancreas-kidney transplant (Ahuja et al., 1997). In addition to concerns of allograft rejection, there were growing concerns over the risks of transplanting HIV infected patients due to the associated high mortality rate brought about by post-operative infectious complications (Stock et al., 2003b). By this point, the discovery of antiretroviral therapy, the first being azidothymidine currently known as zidovudine; revolutionised the management of HIV infection (Yarchoan et al., 1986). The use of antiretroviral therapy

resulted in restoration of CD4 T cells which provided for somewhat delay in HIV disease progression (Fischl et al., 1987). But it wasn't until the late 1990s when HIV was being managed with the 'highly active antiretroviral therapy' (HAART) (Gulick, 1997, Hammer et al., 1997).

HAART regimens often included two nucleoside reverse transcriptase inhibitors (NRTIs) and either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (Oversteegen et al., 2007). More recently, the combination of antiretroviral therapy (cART) could include quad therapy, integrase inhibitors or entry inhibitors (DeJesus et al., 2012, Sax et al., 2012). This provided for immune recovery with much improved CD4 T cell counts and the suppression but not eradication of HIV. HIV kidney transplantation was then revisited and the proposal to allow patients who demonstrated (1) good immune status CD4 counts > 200 cells/mm3 (2) maintained HIV suppression (<50 copies/ml) on cART and (3) no active opportunistic infections or tumors/neoplasms, to be offered kidney transplantation (AST, 2004). There was no guidance on the choice of immunosuppressive therapy but majority used ciclosporin based IS therapy.

The early experience of kidney transplantation in HIV infected patients maintained on cART was quite encouraging with patient and graft survival being comparable to HIV negative patients, (see **Table 4**). On the contrary, rejection was quite prevalent (calculated pooled AR rate of 34% at 1 year, n=240) despite efforts to optimise IS therapy by using triple immunosuppressive agents +/- inclusion induction therapy with mono/polyclonal antibody agents. As so few patients were taking tacrolimus, it was difficult to ascertain if CNI choice had an impact on allograft outcomes. Researchers began to question the efficacy of CNIs brought about by drug interactions with antiretroviral agents (refer to

Chapter 5 for details on CNI/ART drug interactions). Although, a case series of 40 HIV infected kidney transplant recipients who were managed with antiCD25 monoclonal antibody induction therapy and triple IS therapy including ciclosporin, sirolimus and prednisolone; had protocol surveillance allograft biopsies that revealed acute rejection in 22% and subclinical acute rejection in 29% of patients. What was interesting about this report was the observed temporal increase in HIV-1 viraemia (1570 to 70,000 copies/mL), due to drug resistance, that was ascertained through monthly viral load monitoring post-KT. Patients regained HIV virological control by switching antiretroviral therapy agents (Kumar et al., 2005, Sawinski and Murphy, 2008). These findings were in support of previous hypotheses of rejection propagating the HIV virus through CD4 T cell activation (Margreiter et al., 1986a).

Managing the IS/ARV drug interactions in the clinical setting proved quite challenging particularly for those taking protease based antiretroviral therapy that required significant CNI dose reductions (90-99%) when co-prescribed with calcineurin inhibitors (Frassetto et al., 2005, Frassetto et al., 2007, Frassetto et al., 2009). Furthermore, some were concerned about the use of polyclonal or OKT3 antibody agents as their use in the HIV negative transplant population were associated with profound CD4 depletion which made patients more susceptible to opportunistic infections (Trullas et al., 2007). Extra emphasis was placed on avoiding polyclonal antibodies in the HIV infected KT population when Carter et al (2006) reported serious infections requiring hospitalisations in patients that received ATG. However, due to the severity of some of the rejection episodes, ATG was reserved for treatment of severe allograft rejection (Bhagani et al., 2006, Trullas et al., 2010).

In the United Kingdom, the British HIV Association collaborated with British Transplant Society in 2005 to write the national guidance of kidney transplantation in HIV infected patients (Bhagani et al., 2006). This offered guidance on HIV+ patient selection for KT (refer to Chapter 3 for details) but offered no specific guidance on CNI selection, CNI drug concentration targets, anti-infective prophylaxis or antiretroviral therapy choice. It was recommended that centres use local protocols but suggested they classify HIV+ patients as 'high immunological risk'. Although, due to the complexities of CNI/ART drug interactions, BHIVA/BTS 2005 guidelines recommended that HIV infected individuals awaiting transplantation receive a pre-transplant CNI trial as a dose determining strategy to achieve therapeutic CNI drug concentrations post-KT (Bhagani et al., 2006).

Table 4: Summary of acute rejection in kidney transplantation in HIV positive patients (HIV+ prior to transplantation) restricted to publications preceding 2010[a]

Year of Publication	N	Donor type	Induction therapy (N)	Immunosuppression therapy (N)	Acute rejection at 1 year N (%)	1yr Patient survival N (%)	1yr Graft survival N (%)	Reference
Pre-cART								
1980-1985	2	Cadaver	Nil	CsA plus pred	2 (100)	0 (0)	0 (0)	(Rubin et al., 1987, Shaffer et al., 1987)
1981-1986	2	Cadaver	Nil	CsA plus pred	ND	2 (100)	2 (100)	(Dummer et al., 1989)
1984-1987	4	Cadaver	Methylprednisolone	Aza plus pred and/or CsA	2 (50%)	4 (100)	4 (100)	(Ribot and Eslami, 1992)
1986	1*	Cadaver	Nil	Aza plus pred	1 (100)	1 (100)	1 (100)	(Oliveira et al., 1986, Rubin et al., 1987)
1984	2	Cadaver (1) Living (1)	ND	Aza plus pred	ND	2 (100)	1 (100)	(al-Sulaiman et al., 1989)
1997	1	Cadaver (SPK)	Nil	CsA monotherapy (switched to pred. >1yr)	Nil	1 (100)	1 (100)	(Ahuja et al., 1997)
Post-cART								
1997 – 2004	38	ND	Nil (15); ATG (4); OKT3 (3); antiCD25 (16)	CsA (20); Tac (13)	0 (0)	29 (76)	35 (91)	(Qiu et al., 2006)
2000	6	Cadaver (n=4) Living (n=2)	ND	CsA plus MMF plus steroids	4 (67)	6 (100)	6 (100)	(Stock et al., 2001)
2000	1	Cadaver	AntiCD25	Tac plus MMF plus steroids	0 (0)	1 (100)	1 (100)	(Toso et al., 2003a)
2002	12	Cadaver (n=5) Living (n=7)	AntiCD25 (6)	CsA plus SrL plus steroids	4 (33)	12 (100)	12 (100)	(Kumar et al., 2002)
2002	26	ND	ND	ND	10 (38)	24 (92)	23 (88)	(Roland and Stock, 2003)
2003	10	Cadaver (n=6) Living (n=4)	Nil	CsA plus MMF plus steroids	5 (50)	10 (100)	10 (100)	(Stock et al., 2003b)
2000 - 2003	18	Cadaver (n=10) Living (n=8)	AntiCD25 (7)	CsA plus MMF plus steroids (9) SrL plus MMF plus steroids (3) CsA plus SrL plus steroids (2) CsA plus MMF (1); MMF plus steroids (2) MMF alone (1)	12 (70)	17 (94)	15 (83)	(Roland et al., 2008a)
2000 – 2004	22	Cadaver (n=21) Living (n=1)	AntiCD25 and polyconal antibodies (N, ND)	Majority on Tac plus MMF plus steroids (N, ND)	8 (38); (4 Tac, 1 CsA, 3 Other)	22 (100)	17 (77)	(Trullas et al., 2010)
2001 - 2004	40	Cadaver (n=36) Living (n=4)	AntiCD25 (40)	CsA plus SrL plus steroids	9 (22)	33 (82)	28 (71)	(Kumar et al., 2005)
2001 – 2005	10	Cadaver	AntiCD25 (3); ATG (1)	Tac plus MMF plus steroids	4 (40)	10 (100)	9 (90)	(Mazuecos et al., 2002)
2004 – 2007	8	Cadaver (n=7) Living (n=1)	AntiCD25 (8)	CsA plus MMF plus steroids	1 (13)	8 (100)	(88)	(Gruber et al., 2008b)
2005 – 2006	3	Cadaver	ATG (3)	SrL plus MMF plus steroids (2) Tac plus MMF plus steroids (1)	2 (67)	3 (100)	3 (100)	(Trullas et al., 2007)
2007	1	Cadaver (SLK)	AntiCD25	CsA plus pred	0 (0)	1 (100)	1 (100)	(Ballarin et al., 2008)
2008	27	Cadaver (n=15) Living (n=12)	ATG (n=10), antiCD25 (n=11)	CsA or Tac plus MMF or Aza plus steroids (25); dual/mono therapy (12)	9 (33)	27 (100)	27 (100)	(Gasser et al., 2009)
2001 – 2009	20	ND	ND	ND	8 (40)	19 (95)	15 (74)	(Mazuecos et al., 2006)
2005 – 2009	27	Cadaver (n=25) Living (n=2)	AntiCD25 (26), ATG (1)	Tac plus MMF plus Steroids (16) CsA plus MMF plus Steroids (11)	4 (15)	(98)	(96)	(Touzot et al., 2010)
ND	2	Cadaver	Nil	CsA plus MMF plus Steroids (1) Tac plus MMF plus Steroids (1)	1 (50)	2 (100)	2 (100)	(Muller et al., 2006)
2009	7	Cadaver	AntiCD25 (7)	Tac plus MMF plus Steroids (7)	0 (0)	7 (100)	7 (100)	(Billault et al., 2009)

Abbreviations: wk – Weeks, m – Months, yr – Years; MSM – men who have sex with men; KT – kidney transplant; CsA – ciclosporin; Tac – tacrolimus; SrL – sirolimus; Pred – prednisolone; AZT – azidothymidine; IS –immunosuppression; OI – opportunistic infections; ND – no data available; ATG – antithymocyte globulin; antiCD25 – basiliximab or daclizumab; SPK – simultaneous kidney-pancreas transplant; SLK – simultaneous liver kidney transplant

[a]Excludes patients that acquired HIV in the peri- and post-operative period either via donor organ, blood transfusions or other

*This is the first ever HIV positive patient that was transplanted at Hammersmith hospital, London, UK

**Suspected HIV positive prior to transplantation; confirmed HIV+ test performed 2 years post-KT

[†]Triple ART consisted of nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Dual ART included NRTI and NNRTI or PI.

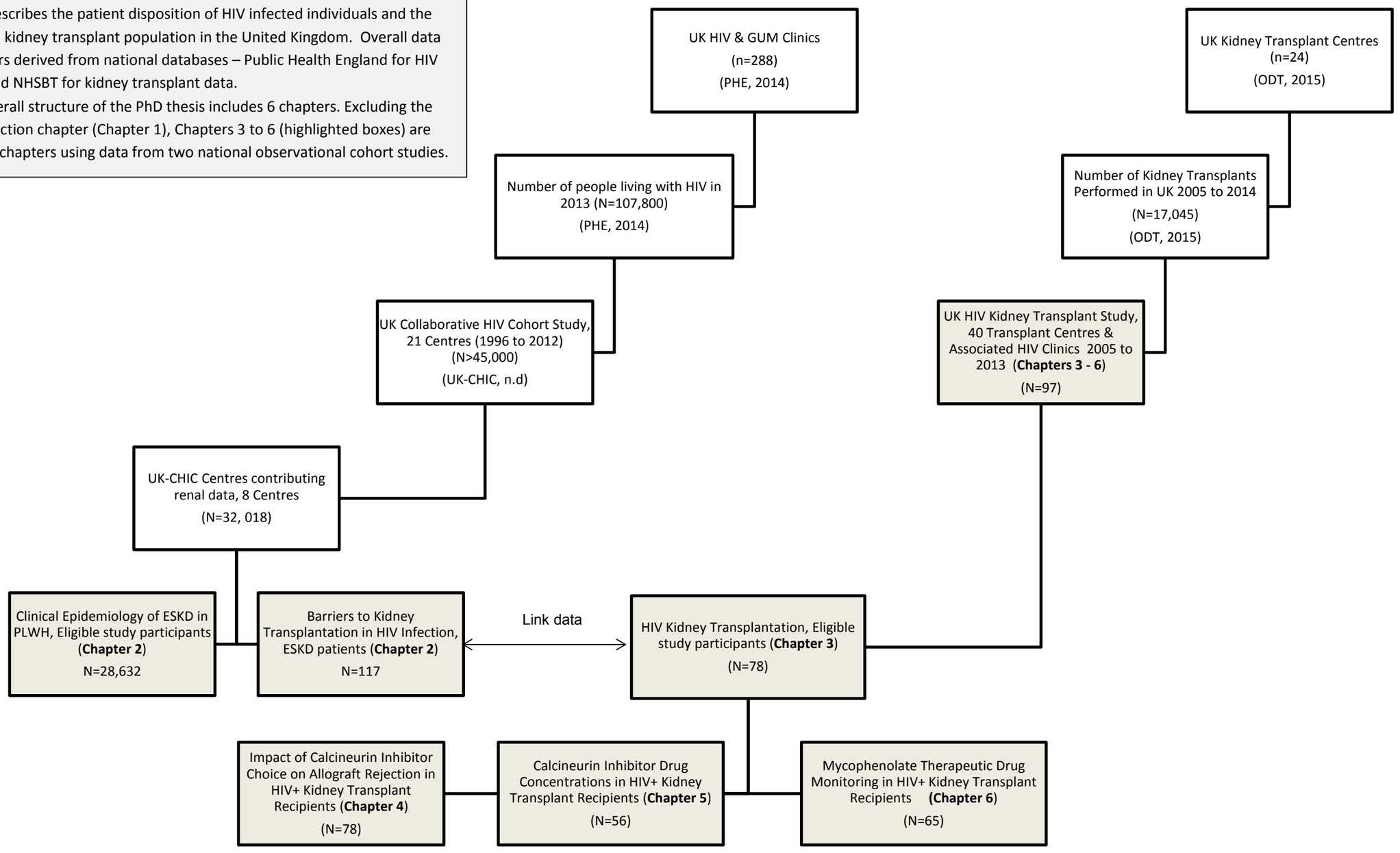
1.6. Focus of Thesis

This thesis will be focused on kidney transplantation in HIV infected individuals in the United Kingdom. First, Chapter 2 will include a description of the clinical epidemiology of end-stage kidney disease in the HIV infected population in the United Kingdom using data from a large UK HIV cohort. Within the same chapter, the barriers to and use of kidney transplantation in the HIV/ESKD patients will be described. To further contextualise the need for kidney transplantation as a treatment modality in the HIV/ESKD population, an investigation was performed to determine whether kidney transplantation affords a survival benefit over dialysis in those who are suitable for KT. In Chapter 3, an evaluation of the clinical outcomes of kidney transplantation in HIV infected patients is performed using data from a national observational cohort study. Chapter 4 to 6 focuses on the post-transplant management of HIV/KT with immunosuppressant drugs. Using data from the national HIV/KT cohort study, an investigation is performed into whether calcineurin inhibitor choice (ciclosporin versus tacrolimus) has an impact on allograft outcomes, specifically allograft rejection in the first year post-HIV/KT (Chapter 4). In Chapter 5, descriptive analyses are peformed to demonstrate the calcineurin inhibitor target whole blood drug concentrations achieved in the first year post-HIV/KT. And finally, an evaluation is performed into the clinical utility of mycophenolate therapeutic drug monitoring in HIV kidney transplantation (Chapter 6).

Thesis Map and Full Patient Disposition

Elements of the PhD Thesis Map

- Map describes the patient disposition of HIV infected individuals and the general kidney transplant population in the United Kingdom. Overall data numbers derived from national databases – Public Health England for HIV data and NHSBT for kidney transplant data.
- The overall structure of the PhD thesis includes 6 chapters. Excluding the introduction chapter (Chapter 1), Chapters 3 to 6 (highlighted boxes) are results chapters using data from two national observational cohort studies.



Chapter 2. Burden of End-Stage Kidney Disease & Barriers to Kidney Transplantation (KT) in HIV Infection

2.1. Introduction

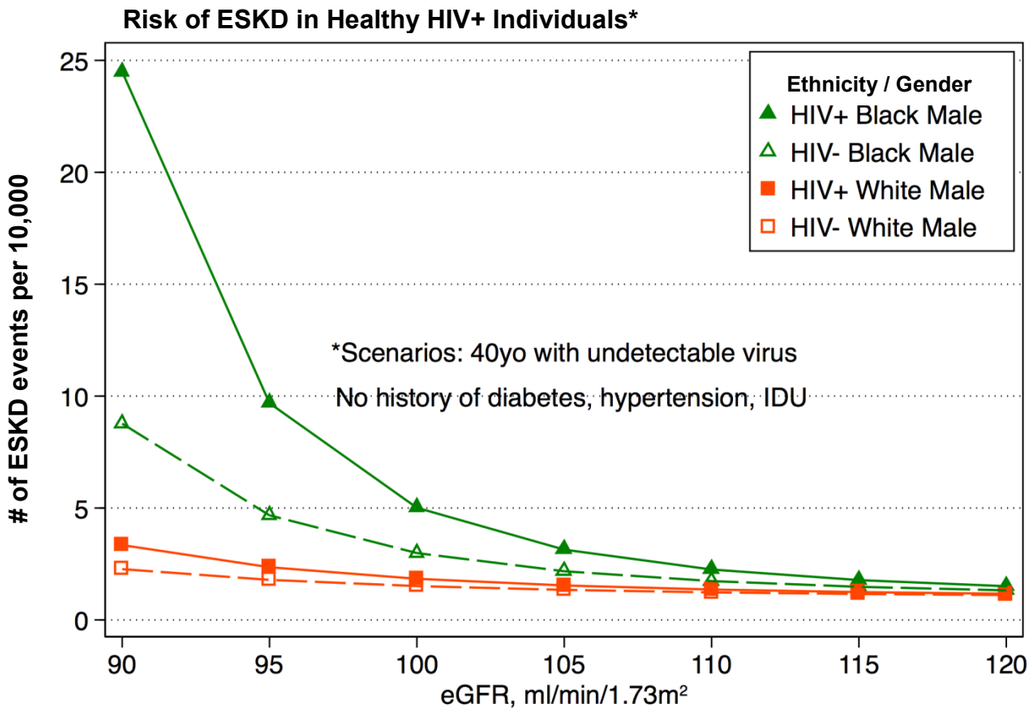
Kidney disease is a common complication in HIV. End-stage kidney disease (ESKD) is a major complication of HIV infection that carries significant morbidity and mortality risks (Choi et al., 2007a, Bansi et al., 2009, Jotwani et al., 2012). In the pre-HAART era, developing ESKD was associated with a high HIV viral load count (Winston et al., 1998, Atta et al., 2005, Jotwani et al., 2012). Other risk factors for HIV ESKD include black ethnicity, intravenous drug user and hepatitis C co-infection (Choi et al., 2007a, Bansi et al., 2009, Jotwani et al., 2012). Traditional causal factors for developing kidney disease have also been implicated in HIV infected patients e.g. diabetes, hypertension, drug toxicity or age, (Weiner et al., 2003). An extensive range of glomerular, vascular and tubulo-interstitial diseases have been observed in HIV infected patients (Berliner et al., 2008, Campbell et al., 2009, Wyatt et al., 2009, Hamzah et al., 2015a).

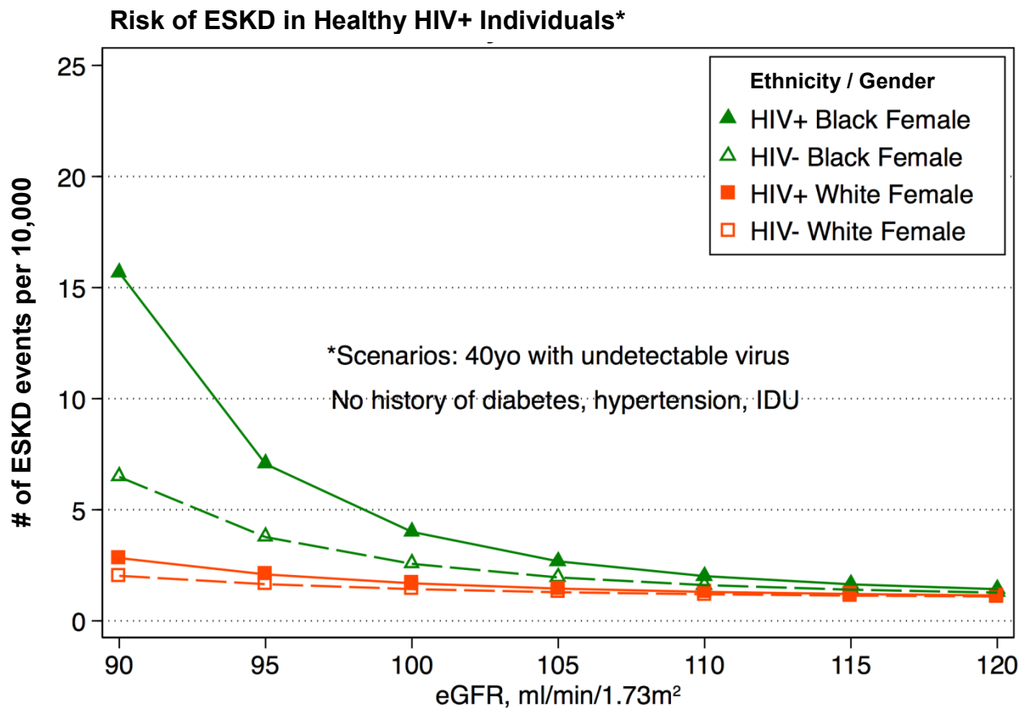
Kidney disease pathology in HIV infection is not completely understood. Direct HIV viral effects, associated antibody and immune responses, as well as release of proinflammatory cytokines by HIV infected lymphocytes and renal cells have all been implicated in HIV renal disease pathogenesis (Bourgoignie, 1990, Mattana et al., 1993, Shukla et al., 1993, Humphreys, 1995, Singhal et al., 1995, D'Agati and Appel, 1997, Klotman, 1999, Conaldi et al., 2000, Ibrahim et al., 2010). The dominant aetiology in this population is HIV-associated nephropathy (HIVAN) (Bansi et al., 2009), a collapsing glomerulopathy which

typically affects immune-compromised patients and presents with severely impaired kidney function and heavy proteinuria (Weiner et al., 2003, Post et al., 2008). Noncollapsing focal and segmental glomerulosclerosis (FSGS), and HIV-associated immune complex kidney disease (HIVICK) and thrombotic microangiopathy (TMA) are other dominant diseases especially with late diagnosis of HIV infection or unavailability or unresponsive HIV treatment with antiretroviral therapy (Weiner et al., 2003). Further, patients presenting with HIVAN are typically of black ethnicity (Bansi et al., 2009, Razzak Chaudhary et al., 2015).

HIV infection is an independent risk factor for developing ESKD (Post et al., 2008, Bansi et al., 2009). In a recent observational cohort study of HIV infected patients (n=42,838) in North America over a 9 year period (2000-2009) observed the risk of ESKD attributable to HIV infection to be 15, 9, 1.1 and 0.8 per 10,000 respectively for black males, black females, white males, and white females with eGFR=90ml/min/1.73m^2, undetectable viral load (<50cps/mL) and CD4 T cell count 750 cells/mm^3 (Muzaale, 2016), (see **Figure 8**). This risk was adjusted for hypertension, IVDU use and diabetes. By comparison, the 15-year risk of ESKD attributable to smoking in comparable HIV negative patients was estimated to be 19, 11, 4, and 3 per 10,000 respectively for black males, black females, white males, and white females with eGFR=90ml/min/1.73m^2.

Figure 8: Risk of Developing End-Stage Kidney Disease in HIV Infected Individuals





Graph shows estimated risk of ESKD in healthy HIV+ individuals stratified by ethnicity and gender. Healthy HIV+ individuals based on 40 year old with undetectable HIV virus (<50 copies/mL), no history of diabetes, hypertension or injectable drug use (Muzaale, 2016).

The availability and use of cART has dramatically improved the outcome of HIV infected patients with ESKD (Lucas et al., 2004, Cremers et al., 2005, Bansi et al., 2009). Although cART may slow the rate of kidney disease progression, the majority of patients develop ESKD within 5 years of diagnosis (Atta et al., 2006, Post et al., 2008). HIV infected individuals of black ethnicity have observed faster progression of kidney disease compared to other ethnicities. Epidemiological studies have reported a 3 to 6 fold increased risk of developing ESKD among patients of black ethnicity compared to other HIV infected individuals (Choi et al., 2007a, Lucas et al., 2008, Jotwani et al., 2012).

In the pre- and early HAART era, dialysis was the only treatment modality offered to HIV/ESKD patients although with poor survival outcomes. There were theoretical concerns that dialysis would enhance HIV viral replication through immune activation and induced pro-inflammatory cytokines (Bingel et al., 1988, Osborn et al., 1989, Herbelin et al., 1990, Takahashi et al., 2000, Mandayam and Ahuja, 2004). Although there was no evidence of increased HIV plasma viral load with dialysis (Ahuja et al., 1999), the one year survival rates for HIV infected patients on dialysis were estimated between 56 to 74% (Ahuja et al., 2002). In the general population, conservative management has been associated with a significantly poorer prognosis compared to dialysis. The survival rate in non-dialysis HIV negative patients has been estimated as low as 6 months, especially with existing comorbidities and cardiovascular disease (O'Connor and Kumar, 2012).

With the improved management of HIV infection with HAART, the uptake of dialysis as a treatment modality of ESKD increased. The prevalence of HIV infection among dialysis units varied from 0% to 39% (Peterman et al., 1986, Morikawa et al., 1988, Chirgwin et al., 1989, Perez et al., 1989, Reiser et al.,

1990, Marcus et al., 1991, Kimmel et al., 1993b, Rao, 2003). Despite this, there were concerns of HIV transmission via dialysis (Marcus et al., 1991, Velandia et al., 1995). However, improper use of dialysis equipment and access needles was implicated as the route of HIV transmission (Velandia et al., 1995). Conservative management was as an alternative option albeit with worse survival rates (Ahuja et al., 2000, Ahuja et al., 2002, Mandayam and Ahuja, 2004). The advancement of medical technologies along with much improved infection control practices greatly reduced the risk of HIV transmission. Furthermore, the risk of transmission of blood borne viruses was directly correlated to the concentration virus in the blood (DOH, 2002, Rao, 2003). Of the blood borne viruses, HIV was considered less infectious (Bingel et al., 1988, DOH, 2002). The UK Department of Health guidelines (2002) recommends (1) testing of HIV only in those at risk (2) segregation of HIV infected patients based on local risk assessments (3) not dialysing HIV infected patients at the same time to avoid cross-infection(DOH, 2002).

Sustained suppression of HIV replication and immune restoration in patients who adhere to cART has allowed successful use of kidney transplantation (KT) in carefully selected patients with ESKD. Typically, these patients had CD4 cell counts >200 cells/mm^3, undetectable HIV RNA levels, and free of opportunistic disease, malignancy, and severe vascular or hepatic co-morbidity (Stock et al., 2003b, Roland, 2004, Bhagani et al., 2006, Stock et al., 2010c, Trullas et al., 2011a, Gathogo et al., 2014). Although overall survival of KT patients has been favourable, it remains unclear whether KT affords a survival benefit over dialysis in those who are suitable for KT.

Purpose of study

This study aims to describe the clinical epidemiology of end-stage kidney disease in HIV infected individuals and, to determine whether kidney transplantation affords a survival benefit over dialysis in those who are suitable for KT. The specific aims of this study include:

Primary aims

Using data from a large UK-based multicentre cohort of HIV-infected individuals, The UK Collaborative HIV Cohort (UK CHIC) Study:

Aim 1: To describe the trends in incidence and prevalence of ESKD and the factors associated with ESKD.

Aim 2: To describe the use of and barriers to kidney transplantation as a treatment modality for ESKD.

Aim 3: To describe survival of HIV infected patients with end-stage kidney disease (HIV/ESKD) managed by KT and dialysis.

Secondary aim

To describe the HIV management with combinational antiretroviral therapy (cART) stratified by treatment modality (dialysis, KT).

2.2. Methods

Study Design

The UK CHIC Study

The United Kingdom Collaborative HIV Cohort (UK CHIC) study is a large longitudinal multi-centre observational cohort study that was initiated in 2001. The original UK CHIC study steering committee was comprised of 13 HIV clinicians, epidemiologists and statisticians from seven HIV clinics; the MRC Clinical Trials Unit and the Health Protection Agency- Communicable Disease Surveillance Centre (HPA-CDSC). Refer to **Appendix B** for full UK CHIC Study Centre List and UK CHIC Steering Committee members. The study received Multi-centre Research Ethics Committee (MREC) and local R&D approvals (UK-CHIC, 2004).

The main aim of UK CHIC study was to monitor HIV infected individuals' health response to HAART. The study aimed to describe the uptake and response to HAART over time, the trends of AIDS-defining illnesses and to identify factors associated with immunological and virological responses to HAART (Bansi, 2011).

UK CHIC Data collection

The study collected routine clinical data on HIV infected individuals over the age of 16 years. Data was collected from 1st January 1996 onwards. 1996 was the year agreed when HAART became available. The original dataset included demographics (date of birth, gender, risk-group, ethnicity), AIDS-defining diagnoses and deaths, CD4 and CD8 T cell counts, HIV viral loads and HAART history (UK-CHIC, 2004).

Table 5 lists all data variables that were collected in the UK CHIC study. More recently, additional data on hepatitis status (B and C) and laboratory markers of HAART-related toxicities (including creatinine) were collected (UK-CHIC, 2004). All data were collected electronically in accordance with the Data Protection Act (1998)(UKParliament, 1998). Data provided were pseudo-anonymised which meant the patient's names were replaced with initials and soundex codes (Mortimer and Salathiel, 1995) and all clinic numbers were replaced with a unique study identifier (UK-CHIC, 2004).

Table 5: Information Collected for the UK CHIC Study (UK-CHIC, 2004)

Demographics	Gender Ethnicity Date of birth Primary risk factor for HIV transmission
Clinical data	Date of first recorded HIV positive test Date of last recorded HIV negative test Date of first clinic visit Date of last clinic visit Date of death Cause of death Date and description of each AIDS-defining event
Laboratory Markers	Date and result of CD4 cell count for all available measurements Date and result of CD8 cell count for all available measurements Date and result of CD4 percentage for all available measurements Date and result of CD8 percentage for all available measurements Date and result of HIV RNA viral load for all available measurements
Antiretroviral Treatment	Date of starting all antiretroviral drug Date and reasons (maximum 3) for stopping all antiretroviral drug
PCP Prophylaxis	PCP prophylaxis drug Date of starting PCP prophylaxis Date of stopping PCP prophylaxis
Hepatitis	Date of hepatitis test Hepatitis test Hepatitis test result (negative/positive/unknown)
Laboratory marker	**Normal range and units**
Total cholesterol	<5.2 mmol/l
HDL-cholesterol	>1 mmol/l
LDL-cholesterol	<4 mmol/l
Triglycerides	<2.3 mmol/l
Lactate	0.5-2.0 mmol/l
Glucose	Fasting <5 days: 0.7-4.2 mmol/l
	Fasting >5 days: 2.9-5.3 mmol/l
Aspartate aminotransferase	5-40 IU/l
Alanine transaminase	5-40 IU/l
Albumin	35-50 g/l
Bilirubin	5-17 Umol/l
Alkaline phosphate	42-128 IU/l
Gamma GT	Male: 9-54 IU/l
	Female: 8-35 IU/l
Urea	3.0-6.5 mmol/l
Creatinine	60-97 µmol/l
White blood count	3.7-9.5 x 109 cells/l
Haemoglobin	Male: 13.5-17.5 g/dl
	Female: 11.5-15.5 g/dl
Platelets	140-400 x 109 cells/l

Data Quality Assurance

Database accuracy

There were several steps followed for data quality assurance carried out by the study manager. First, an extensive range of queries were applied to the data from each centre to identify missing, invalid, illogical or conflicting demographic data. An example of this, an HIV-positive test date occurring prior to a HIV-negative test date. Any inconsistencies with the data were resolved where possible by each centre through clinic databases or medical records. Where accurate information was obtained, this information was updated on both the source and UK CHIC database (UK-CHIC, 2004).

Database linkage to death registries

Patients lost to follow-up were linked to the UK death registries i.e. Office for National Statistics (ONS) for England and Wales, and the General Registrar Office for Scotland (GRO). Information used to link to death registries included date of birth, first name initial, soundex and gender. Linkage to the death registries also helped with completing missing data, 'date of death' (UK-CHIC, 2004).

Database audit

Regular database audits were carried out to ascertain the accuracy of information held. The auditing process included a random selection of 1% of patient records from each centre. The centre investigator would then recreate the dataset using local databases and medical records. The final dataset was then cross checked with the audit data and then fed back to the individual centres to rectify any issues that were identified. Accurate data was defined as

exact match for date of birth, gender, first-name initial, soundex, ethnicity, HAART history and country of origin. Dates for HIV-negative and HIV-positive tests were considered accurate if within one year of each other. Date first attended clinic or 'date first-seen' and dates for initiating/stopping antiretroviral therapy were considered accurate if within one month of each other (UK-CHIC, 2004).

Duplication

Due to the possibility of patients attending more than one centre for their HIV care, the database was checked for duplicate records. Initially the database was searched for exact match for soundex code and date of birth. Patients were excluded from further matching processes in the instances where the patient was known to have transferred to another centre. If duplicates were found, then other clinical or demographic data were searched for matches. HIV diagnosis date was considered a match if within one year. Dates were considered a match if within one month for date last seen and date of death. Duplicates identified within the same centre were deemed indeterminate and considered non-matches; and no further checks made. Manual checks were carried out when the soundex and date of birth matched exactly or soundex and date of birth did not match exactly. Once all the checks were performed, true duplicate records were merged and where information was insufficient to determine if two records matched, these records remained on the database as distinct individual records. The initial data check of the UK CHIC study identified 1185 duplicate records representative of 8.6% of the cohort (N=13, 833). These duplicate records were merged. Of the 1185 duplicate records, 1078 (91.1%) had attended only two centres; 95 (8.0%) attended three centres and 12 (1.0%) had attended four

different centres. When records were merged, any inconsistences in the data collected were resolved by local investigators (UK-CHIC, 2004).

The UK CHIC / ESKD Study

By the start of the UK CHIC / ESKD study, there was one additional centre contributing data to the UK CHIC database. The data used for this chapter's analyses were derived from eight centres (**Appendix B**) until 31/12/2012. The study was approved by local NHS research and development (R&D) departments.

Definitions

Permanent renal replacement therapy (pRRT) was defined as either commenced on dialysis or having received a kidney allograft for the management of ESKD.

End-stage kidney disease was defined as having an estimated glomerular filtration rate (eGFR) <15ml/min for more than 3 months.

Inclusion Criteria

Patients were restricted to those with at least one serum creatinine value.

HIV infected individuals with ESKD were identified from the UK CHIC database using the following algorithm:

1. Using all available serum creatinine values and adjusting for IDMS (isotope dilution mass spectrometry), data wer converted to estimated glomerular filtration rates (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation (Gupta et al., 2005, Grinyo et al., 2009).

2. Patients with stage 5 chronic kidney disease, i.e. an eGFR <15 mL/min/1.73m^2, for >3 months were identified (Bansi et al., 2009).
3. Patients were reviewed by study investigators and included if they had commenced pRRT.
4. Additional data checks were performed where local clinicians at the HIV and associated renal centres were asked to identify patients on pRRT using local databases and medical records.
5. The pRRT list generated from UK CHIC was cross matched to the clinician identified list.

Additional ESKD Verification Criteria

Clinician documented diagnosis of haemodialysis, peritoneal dialysis or kidney transplantation on data collection form.

Exclusion Criteria

1. Patients without serum creatinine data were excluded from the analyses.
2. Patients that had died prior to 2005.
3. Patients that dialysed less than 3 months.

HIV Kidney Transplantation Assessment Criteria

Inclusion criteria

Assessment for eligibility of KT was carried out retrospectively and applied the following criteria

(1) Transplant status at last date of follow-up (FU) i.e. transplanted or not transplanted. If patients were transplanted it was assumed that they were suitable for KT however, date of suitability was determined by criteria 2 below.

(2) HIV viral suppression (<50 cps/ml) status. This was determined by looking retrospectively to the date that the patient had HIV viral suppression (<50cps/ml) > 6 months and / or initiated pRRT.

(3) Medical reason for ineligibility. Of those not transplanted clinicians at the local centres reviewed patients and indicated if there was any medical reason (s) that precluded transplantation.

Exclusion criteria

Other local or national criteria on wait-listing for kidney transplantation were not applied to the selection criteria for suitability of KT in this study. This included listing or de-listing dates and CD4 T-cell count > 200 cells/mm^3.

Patients who would had become eligible or died pre-2005 were excluded from the assessments for eligibility of KT. Patients transplanted pre-2005, when transplantation was not being offered as a treatment modality for HIV ESKD patients, and those with missing information were also excluded.

Table 6: List of AIDS Defining Illnesses

(Rogstad et al., 2006, Mitchell et al., 2011)

	AIDS-defining conditions	Other conditions where HIV testing should be offered
Respiratory	Tuberculosis Pneumocystis	Bacterial pneumonia Aspergillosis
Neurology	Cerebral toxoplasmosis Primary cerebral lymphoma Cryptococcal meningitis Progressive multifocal leucoencephalopathy	Aseptic meningitis/encephalitis Cerebral abscess Space occupying lesion of unknown cause Guillain–Barré syndrome Transverse myelitis Peripheral neuropathy Dementia Leucoencephalopathy
Dermatology	Kaposi's sarcoma	Severe or recalcitrant seborrhoeic dermatitis Severe or recalcitrant psoriasis Multidermatomal or recurrent herpes zoster
Gastroenterology	Persistent cryptosporidiosis	Oral candidiasis Oral hairy leukoplakia Chronic diarrhoea of unknown cause Weight loss of unknown cause Salmonella, shigella or campylobacter Hepatitis B infection Hepatitis C infection
Oncology	Non-Hodgkin's lymphoma	Anal cancer or anal intraepithelial dysplasia Lung cancer Seminoma Head and neck cancer Hodgkin's lymphoma Castleman's disease
Gynaecology	Cervical cancer	Vaginal intraepithelial neoplasia Cervical intraepithelial neoplasia Grade 2 or above
Haematology		Any unexplained blood dyscrasia including: • thrombocytopenia • neutropenia • lymphopenia
Ophthalmology	Cytomegalovirus retinitis	Infective retinal diseases including herpesviruses and toxoplasma Any unexplained retinopathy
ENT		Lymphadenopathy of unknown cause Chronic parotitis Lymphoepithelial parotid cysts
Other		Mononucleosis-like syndrome (primary HIV infection) Pyrexia of unknown origin Any lymphadenopathy of unknown cause Any sexually transmitted infection

Statistical analysis

Statistical analyses in this chapter were performed using SAS (version 9.3) and STATA (version 11.1). Before statistical analysis, data were checked for normal distribution. Where there was normal distribution, descriptive statistics including means and standard deviations were used. Medians and interquartile ranges were used for skewed data. Frequencies and proportions were used to describe categorical data. Wilcoxon-ranksum test was used to compare medians; Z-tests were used to compare means; and two-sided chi-squared (X^2) or Fisher's exact test to compare proportions. Statistical significance level was considered at $p < 0.05$.

Longitudinal Analysis of the Trends in HIV/ESKD

Trends of ESKD in the HIV infected population were described over time from 1998-2012 in terms of prevalence, incidence and cumulative incidence rates and stratified by ethnicity (black (black-African, black-Caribbean, and black-other)) and treatment modality (dialysis and kidney transplantation).

The incidence rate was used to describe the number of new ESKD cases in the entire HIV infected cohort that met the inclusion criteria for the UK CHIC/ESKD study over the study period. Each HIV infected individual contributed time from cohort entry which was taken as date of HIV diagnosis to date of last clinic visit or 31/12/2012. Study participants were censored at death or date of last clinic visit if lost to follow-up. The incidence rate then allowed me to explore the relationship between the risk factors and ESKD.

The prevalence was used to describe the proportion of individuals in the entire HIV infected cohort that were included in the UK CHIC/ESKD study. The prevalence provided information on the burden of ESKD in the studied cohort. To describe the trends in ESKD, both the incidence and prevalence were calculated for select time points during the study period i.e. 2000-2001, 2002-2003, 2004-2005, 2006-2007, 2008-2009, 2010-2011. ESKD incidence and prevalence in the different strata was calculated per 100 person-years of follow-up (PYFU).

Cumulative incidence was estimated by a competing-risks regression model, treating death as a competing risk, stratified by ethnicity and compared with Wald tests. The cumulative incidence described the proportion of the HIV infected UK CHIC population included in the analyses that were at risk of developing ESKD over the entire cohort follow-up time. Death was included in the regression model as a competing risk as it may have confounded the estimates of ESKD risk. For example, a patient may have died before developing ESKD therefore the overall estimates would be under-represented.

Factors Associated with HIV/ESKD

Factors associated with ESKD were determined using Poisson regression. The Poisson regression model was selected as the event i.e. ESKD was a binary outcome. This model determined the rate at which ESKD occurred in the HIV infected cohort and allowing for the individual follow-up time which differed between study participants over the study period.

When performing the analyses to identify the factors associated with ESKD analyses; the time dependent covariates considered were age (per 10 years older), HIV viral load (per log_{10} copies/ml), and CD4 T cell count (per 50 cells/mm^3). The time independent covariates were gender, ethnicity, mode of HIV acquisition, HBV/HCV co-infection status and if initiated cART at last clinic visit. Following univariable analyses all covariates with a p value of <0.05 were considered for entry into the multivariable model.

Survival Analyses

Patient survival was estimated by the Kaplan-Meier method, and survival time across the stratified groups (unsuitable for KT and suitable for KT (pre- and post-KT)) and was compared with log-rank tests. The time of analysis was taken from start date of pRRT until the date of last clinic visit or 31/12/2012.

For the evaluation of mortality, the date of last follow-up or 31/12/2012 or date of KT was used and; the cohort was stratified into three groups i.e. transplanted (Post-KT) vs. not transplanted – suitable (Pre-KT) vs. unsuitable for KT. The post-KT population contributed both (1) time of follow-up from the date they were suitable for KT until date of KT and (2) time from KT to date of last follow-up or 31/12/2012.Crude mortality rates were adjusted for age and ethnicity. Crude mortality rates with 95% CI were estimated for each of the stratified groups described above.

Bias Associated with Missing data

To address missing data and reduce bias or standard errors, sensitivity analyses were performed by the last observation carried forward to impute missing values (Horton and Kleinman, 2007).

Cross-sectional data analyses

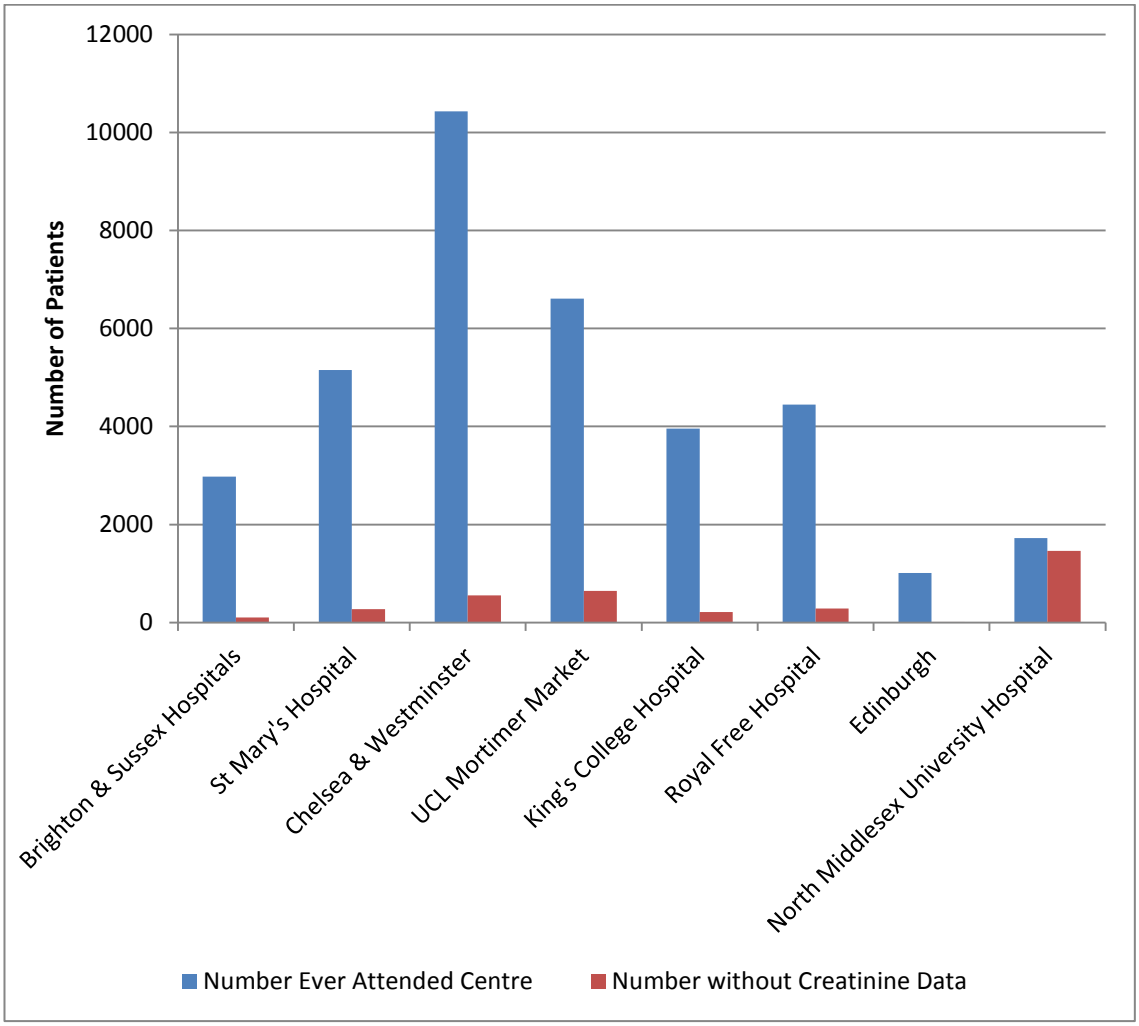
Descriptive analyses (frequency and proportions) were used to describe antiretroviral drug regimens prescribed in the identified HIV/ESKD cohort. Initially, patients were stratified into protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimens. A further stratification was then applied for those exposed to atazanavir vs. tenofovir vs. other at any point from date of HIV diagnosis up to date of last clinic visit. A cross-sectional review was then carried out at most recent visit for three time points: pre-KT, at KT, and post-KT.

2.3. Results

HIV/ESKD Patient Characteristics

Between January 2000 and December 2011, there were 32, 018 HIV infected individuals from eight participating HIV clinics that contributed data to the UK CHIC study. Refer to **Figure 10** for full patient disposition. Of those HIV infected individuals that ever attended each centre, 10.6% (3, 388) did not contribute any creatinine data and therefore excluded from further analyses, (see **Figure 9**).

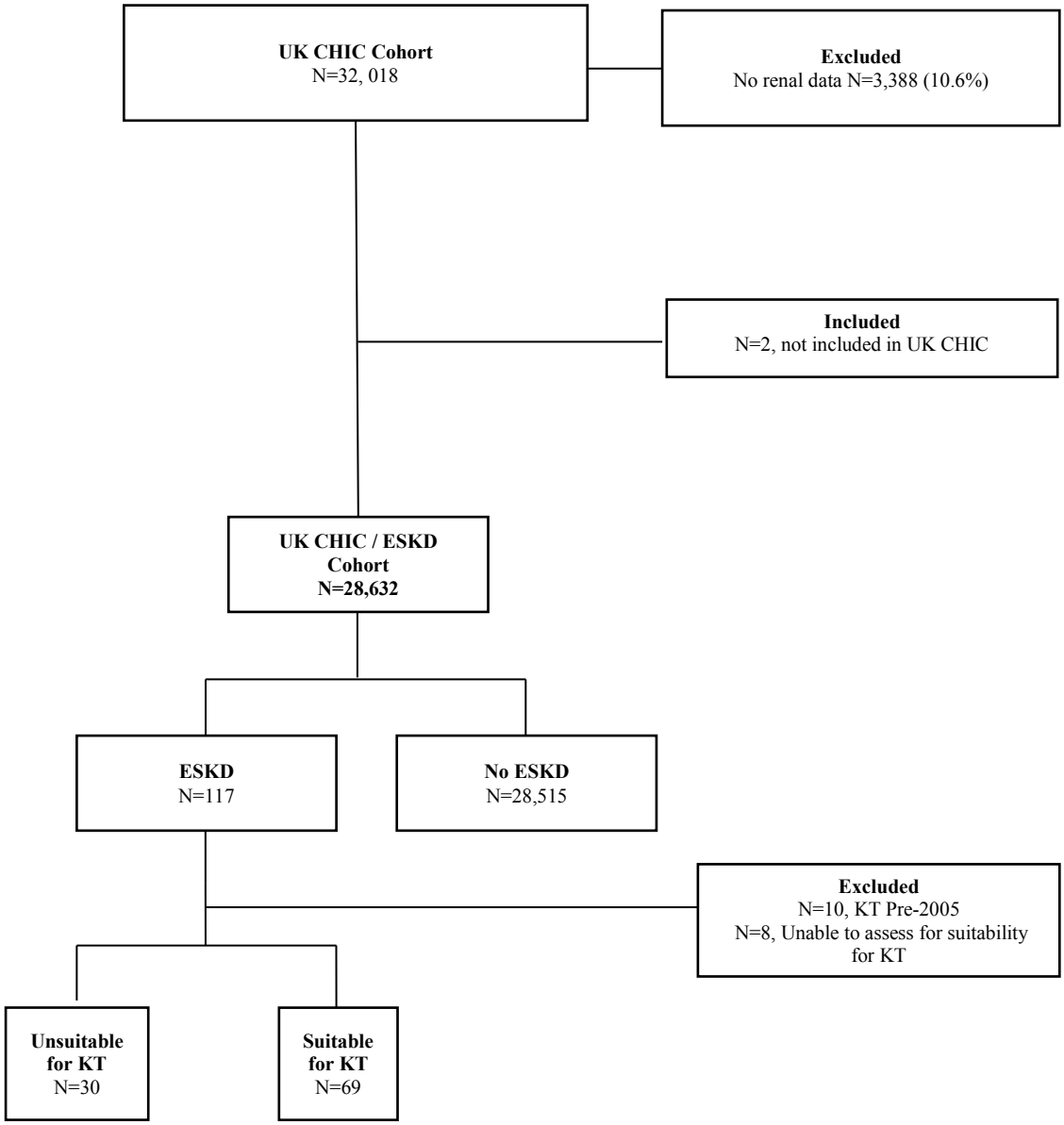
Figure 9: Number of HIV Infected Individuals in UK CHIC Study Stratified by Centre



Graph represents the total number of patients that ever attended each of the eight HIV clinics (blue bars) that contributed data to the UK CHIC study. Of those included in the UK CHIC study, a number of patients had missing creatinine data (red bars)

Of the excluded patients (N=3,388), the proportions to ever attend each participating centre were as follows: North Middlesex University hospital (43.1%); UCL Mortimer Market (19.1%); Chelsea and Westminster (16.4%); Royal Free hospital (8.4%); St Mary's hospital (8.0%); King's College hospital (6.4%); Brighton & Sussex hospitals (3.1%); and Edinburgh (0.4%). There were an additional two patients identified from Edinburgh centre that had not started contributing data to UK CHIC studythat were included in the analyses.

Figure 10: Full Patient Disposition for HIV/ESKD Cases Identified from the UKCHIC Study



Characteristics of HIV+ patients included and excluded from the analyses

An initial comparative analysis of the patient characteristics of those included compared to the excluded group in the UK CHIC/ESKD study was performed, (see **Table 7**). The included/excluded groups demonstrated significant differences in all patient characteristic parameters. Within the excluded group (N=3,388), there was a higher proportion of patients that were male (61.9%), of black ethnicity (49.1%), heterosexual (51.5%), not on ART (77.3%) and had not been tested for hepatitis B (85.3%) or C (87.5%).

Table 7: Characteristics of Included/Excluded HIV+ Patients in UK CHIC/ESKD Study

Characteristic		**Included**	**Excluded**	P
N		28630	3388	
Age, median(IQR)	years	35 (29, 41)	35 (29, 42)	0.003
Sex, n (%)	Male	22516 (78.6)	2097 (61.9)	<0.001
	Female	6114 (21.4)	1291 (38.1)	
Ethnicity, n (%)	Black	7307 (25.5)	1662 (49.1)	<0.001
	Other	20489 (71.6)	1423 (42.0)	
	Unknown	834 (2.9)	303 (8.9)	
Exposure, n (%)	Men who have sex with	17060 (59.6)	995 (29.4)	<0.001
	men	8573 (29.9)	1744 (51.5)	
	Heterosexual	2997 (10.5)	649 (19.2)	
	Other			
CD4 count, median(IQR)	cells/mm^3	354 (200, 527)	300 (140, 480)	<0.001
Viral load, median(IQR)	log_{10}copies/ml	3.9 (1.7, 4.8)	3.9 (2.6, 4.8)	<0.001
ART, n (%)	No	19513 (68.2)	2620 (77.3)	<0.001
	Yes	9117 (31.8)	768 (22.7)	
Hepatitis B co-infection, n	No	9441 (33.0)	454 (13.4)	<0.001
(%)	Yes	551 (1.9)	43 (1.3)	
	Not tested	18638 (65.1)	2891 (85.3)	
Hepatitis C co-infection, n	No	8706 (30.4)	368 (10.9)	<0.001
(%)	Yes	675 (2.4)	55 (1.6)	
	Not tested	19249 (67.2)	2965 (87.5)	

Characteristics of HIV/ESKD patients

There were a total of 28, 632 patients included in the final analyses. In this group, there were a higher proportion of patients that were male (78.6%), of other ethnicity (71.6%), men who have sex with men (59.6%), not taking ART (68.2%), and not tested for hepatitis B (65.1%) or C (67.2%). The median (IQR) number of available creatinine measurements was 16 (5, 30) and 18 (7, 35) for those of black and other ethnicity respectively ($p<0.0001$). The median (IQR) follow up was 6.4 (2.5, 11.1) years, during which 1732 individuals (6.0%) died.

Using the selection criteria discussed above, 117 patients (including the two additional patients that did not contribute data to the UK CHIC study) were identified as having received permanent renal replacement therapy at the associated renal centres. The clinical characteristics of 115 ESKD cases (0.4%) present in the UK CHIC study dataset and the 28,515 patients without ESKD are shown in **Table 8** Baseline patient characteristics differed between those with ESKD and those with no ESKD for all selected covariates except for time since HIV diagnosis, HIV viral load and hepatitis B/C co-infection. At cohort entry there were a significantly higher proportion of patients in the ESKD group that were older, of black ethnicity, ever had an AIDS (CDC-C) illness, lower nadir and overall CD4 T cell count, lower estimated glomerular filtration rate and being maintained on ART.

Table 8: Characteristics of patients according to ESKD status over follow-up

		ESKD	No ESKD	P
		at cohort entry		
N		115	28515	
Age, median (IQR)	years	38 (32, 44)	35 (29, 41)	0.001
Gender, n (%)	male	80 (69.6)	22436 (78.7)	0.02
Ethnicity, n (%)	black	73 (63.5)	7234 (25.4)	<0.0001
Time since HIV diagnosis, median (IQR)	years	1.0 (0.1, 3.8)	0.7 (0.0, 5.7)	0.43
AIDS (CDC-C), n (%)		28 (24.3)	3401 (11.9)	0.007
CD4 nadir, median (IQR)	cells/mm^3	139 (38, 255)	257 (110, 430)	<0.0001*
CD4 count, median (IQR)	cells/mm^3	218 (89, 357)	355 (201, 528)	<0.0001**
Viral load, median (IQR)	log_{10} copies/ml	4.0 (1.7, 4.8)	3.9 (1.7, 4.8)	0.28†
eGFR, median (IQR)	ml/min/1.73m^2	22 (11, 57)	103 (89, 115)	<0.0001††
Antiretroviral therapy, n (%)	yes	52 (45.2)	9065 (31.8)	0.002
Hepatitis B surface antigen positive, n (%)		3 (2.6)	548 (5.5)	0.56 [x]
Hepatitis C antibody positive, n (%)		4 (3.5)	671 (7.2)	0.65 [xx]

* n=19257, **n=17982, † n=18921, ††n=15117, [x] n=10071, [xx] n=9455, ^ incomplete data for n=1 patient

KT = kidney transplantation; pRRT = permanent renal replacement therapy

HIV associated nephropathy (HIVAN) was confirmed on biopsy as the primary renal diagnosis in 46% (N=54) of the ESKD patients. 80% of the HIVAN cases were in patients of black ethnicity (N=43/54). Other renal diagnoses are described in **Table 9**.

Table 9: Aetiology of Kidney Disease in HIV/ESKD Individuals

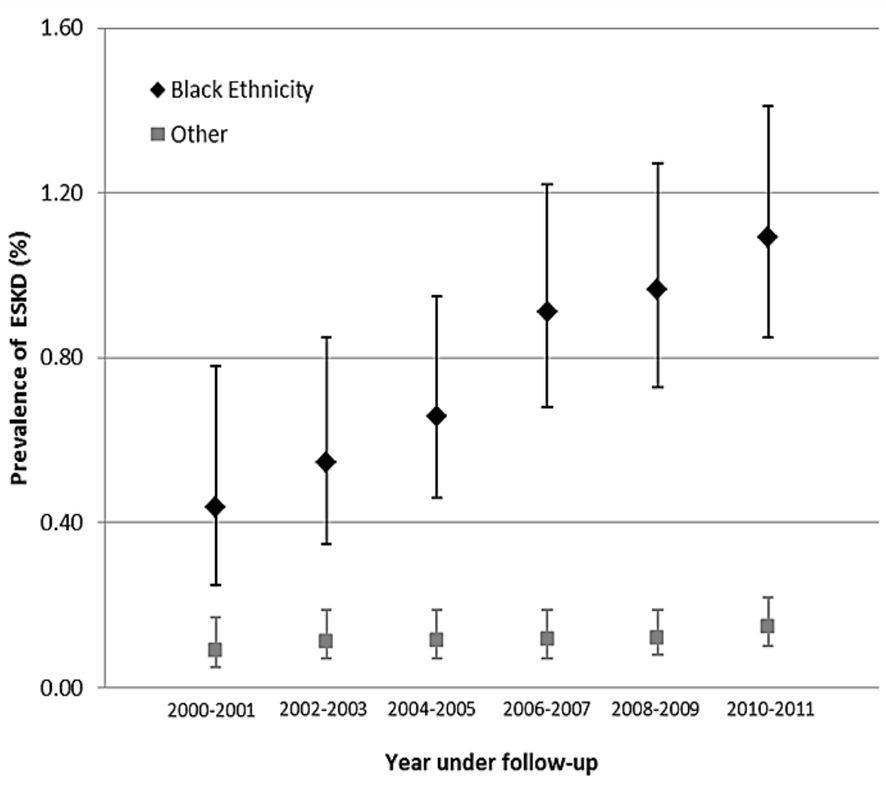
Aetiology of Kidney Disease	N (%)
HIV Associated Nephropathy (HIVAN)	54 (46)
Idiopathic chronic kidney disease (ICKD)	15 (13)
Diabetic Nephropathy	13 (11)
Amyloid	6 (5)
Focal segmental glomerulosclerosis (FSGS)	2 (2)
Other • **Ascending chronic pyelonephritis** • **Acute tublar necrosis (ATN)** • **Autosomal dominant polycystic kidney disease** • **Congenital kidney disease** • **Congenital posterior urethral valves** • **Drug toxicity** • **Hypertensive nephropathy** • **Haemolytic-uremic syndrome (HUS)** • **Interstitial fibrosis and tubular atrophy (IFTA)** • **Polycystic Kidney disease (PCKD)** • **Reflux nephropathy** • **Renal dysplasia** • **Renal-vascular disease** • **Scarred kidneys** • **Small kidneys** • **Single kidney atherosclerosis** • **Tubulointerstitial nephritis (TIN)** • **Unknown**	27 (23)

Prevalence and Incidence of ESKD

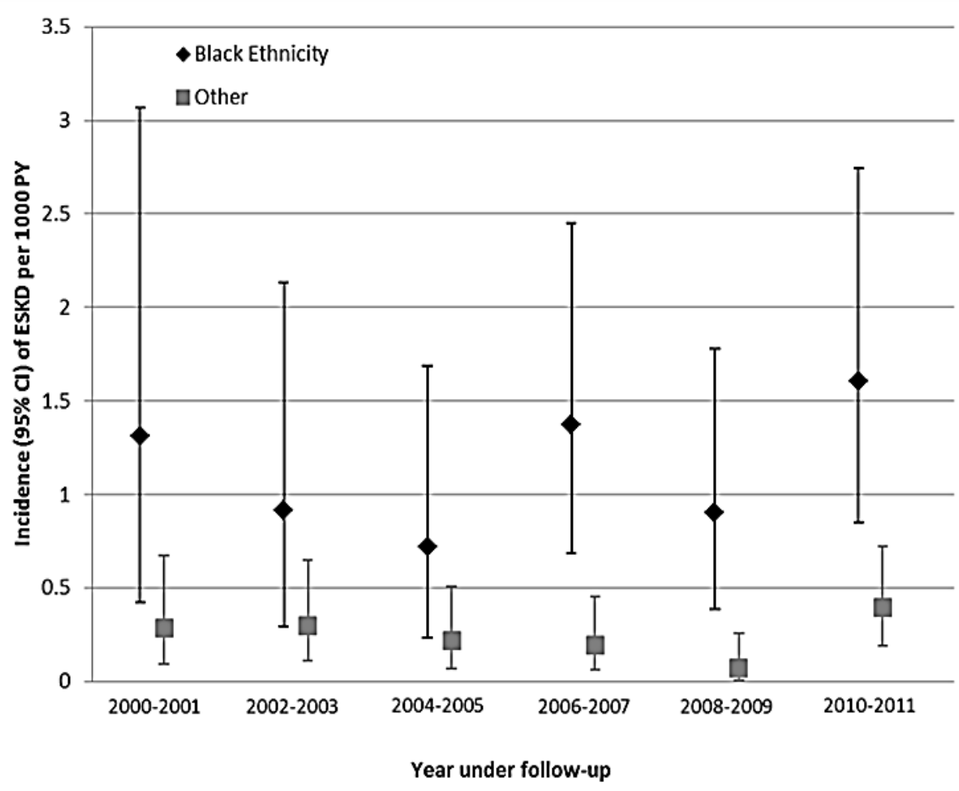
During the study period, there was a steady increase in ESKD prevalence observed among patients of black ethnicity (from 0.44% (95% CI 0.25%, 0.78%) in 2000/1 to 1.09% (0.85%, 1.41%) in 2010/11, p=0.008) while the ESKD prevalence among those of other ethnic groups remained stable (0.09% (0.05%, 0.17%) to 0.15% (0.10%, 0.22%), p=0.87 (see **Figure 11A**). After adjusting for age, the prevalence of ESKD appeared to increase over time in those of black ethnicity (0.36% (0.18%, 0.65%) 2000/1 to 1.35% (1.01%, 1.77%) 2010/11), but not in those of other ethnic groups (0.09% (0.04%, 0.18%) to 0.11% (0.07%, 0.17%)). For both patient groups, the incidence of ESKD remained unchanged throughout the study period (see **Figure 11B**).

Figure 11: Trends of ESKD in HIV Infected Individuals

A. Prevalence (%) of ESKD with 95% confidence intervals in those of black and other ethnicities, stratified by year of follow-up



B. Incidence of ESKD in those of black and other ethnicities, stratified by year of follow-up



Factors Associated with ESKD

Excluding antiretroviral drug choice, all other covariates in **Table 10** were included in the Poisson regression analyses. Results from univariable analyses were statistically significant for all covariates except for HIV viral load, having started combination ART, hepatitis B – the not tested group, and hepatitis C – the co-infected and not tested groups. Statistically significant univariable covariates were included in the multivariable analyses with the exception of gender and exposure group as these factors were considered highly correlated with ethnicity in the UK CHIC cohort. Factors that were independently associated with developing ESKD were age (IRR per 10 years older, 1.50 (1.20, 1.87)), black ethnicity (5.45 (3.42, 8.70)), CD4 count (per 50 cells/mm^3 higher, 0.91 (0.87, 0.95)) and hepatitis B and C co-infection (respectively, 2.89 (1.35, 6.19) and 3.03 (1.41, 6.54)), **Table 10**.

For the continuous variables HIV viral load and CD4 T cell count, there were missing data for several time points during the follow-up period. In order to reduce possible bias brought about by missing data and to confirm validity of findings, sensitivity analyses using the last observation carried forward (LOCF) method (Cozzi Lepri et al., 1998) was performed. Findings from these analyses remained the same confirming that factors including age, black ethnicity, CD4 count, and hepatitis B and C co-infection were independently associated with developing ESKD, **Table 11**.

Table 10: Results from univariable and multivariable Poisson regression analyses to identify factors associated with ESKD

	Univariable Models		Multivariable Model	
	IRR (95% CI)	**P**	**IRR (95% CI)**	**P**
Age				
per 10 years older	1.28 (1.02, 1.59)	0.030	1.50 (1.20, 1.87)	0.0003
Gender				
Male	1.00	.	excluded	
Female	1.78 (1.09, 2.89)	0.021		
Ethnicity				
Black	4.88(3.11, 7.67)	<0.0001	5.45 (3.42, 8.70)	<0.001
Other	1.00	.	1.00	.
Mode of acquisition				
Men who have sex with men	1.00	.		
Heterosexual	5.44 (3.25, 9.10)	<0.0001	excluded	
Other	4.07 (1.92, 8.65)	0.0003		
CD4 count				
per 50 cells/mm^3 higher	0.91 (0.87, 0.95)	<0.0001	0.91 (0.87, 0.95)	<0.0001
HIV RNA				
per log_{10} copies/ml higher	1.17 (0.97, 1.14)	0.11		
Started cART				
No	1.00	.		
Yes	1.63 (0.81, 3.26)	0.17		
HBV				
No	1.00	.	1.00	.
Yes	3.59 (1.68, 7.65)	0.001	2.89 (1.35, 6.19)	0.006
Not Tested	1.46 (0.91, 2.35)	0.12	1.53 (0.82, 2.85)	0.18
HCV				
No	1.00	.	1.00	.
Yes	1.97 (0.93, 4.17)	0.077	3.03 (1.41, 6.54)	0.005
Not Tested	1.18 (0.72, 1.93)	0.51	0.85 (0.44, 1.65)	0.64

IRR=Incidence Rate Ratio; CI=Confidence Interval; P=p-value

Table 11: Results from univariable and multivariable Poisson regression analyses to identify factors associated with ESKD with sensitivity analyses, with last CD4 count/VL carried forward

Characteristics	Univariable Models		Multivariable Model	
	IRR (95% CI)	**P**	**IRR (95% CI)**	**P**
Age				
per 10 years older	1.28 (1.02, 1.59)	0.030	1.49 (1.17, 1.89)	0.001
Gender				
Male	1.00	.	excluded	
Female	1.78 (1.09, 2.89)	0.021		
Ethnicity				
Black	4.88(3.11, 7.67)	<0.0001	4.96 (3.03, 8.11)	<0.001
Other	1.00	.	1.00	.
Mode of acquisition				
Men who have sex with men	1.00	.		
Heterosexual	5.44 (3.25, 9.10)	<0.0001	excluded	
Other	4.07 (1.92, 8.65)	0.0003		
CD4 count				
per 50 cells/mm^3 higher	0.90 (0.86, 0.95)	<0.0001	0.89 (0.84, 0.94)	0.0001
HIV RNA				
per log_{10} copies/ml higher	1.17 (0.99, 1.39)	0.073	1.14 (0.95, 1.37)	0.15
Started cART				
No	1.00	.		
Yes	1.63 (0.81, 3.26)	0.17		
HBV				
No	1.00	.	1.00	.
Yes	3.59 (1.68, 7.65)	0.001	2.77 (1.29, 5.94)	0.009
Not Tested	1.46 (0.91, 2.35)	0.12	1.36 (0.71, 2.61)	0.35
HCV				
No	1.00	.	1.00	.
Yes	1.97 (0.93, 4.17)	0.077	2.92 (1.35, 6.31)	0.007
Not Tested	1.18 (0.72, 1.93)	0.51	0.90 (0.45, 1.80)	0.76

IRR=Incidence Rate Ratio; CI=Confidence Interval; P=p-value

Kidney Transplantation (KT) as a Treatment Modality in HIV Infection

In this section using the 117 ESKD cases identified, analyses were performed to assess the barriers to and use of kidney transplantation as a treatment modality in HIV infection. Subsequent analyses were performed to describe the survival of HIV infected patients with ESKD managed by KT and dialysis.

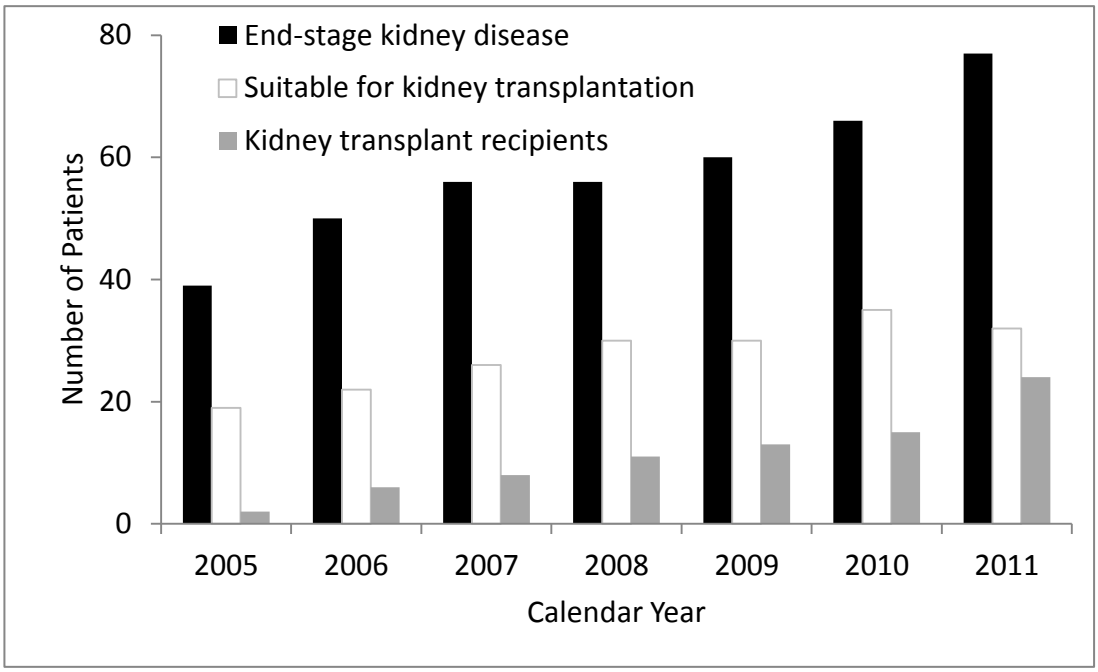
Barriers to Kidney Transplantation in HIV Infection

Of the 117 ESKD cases identified, 10 patients that received KT pre-2005 and those with insufficient information to be assessed for suitability (N=8), were excluded from further analyses. With the use of the KT assessment criteria outlined earlier (section 2.2), of the remaining 99 patients, 30 were not suitable for kidney transplantation. Viral non-suppression (HIV VL > 400 cps/ml) as a reason for ineligibility was noted in 53% (N=16/30) of the cases. Two patients declined to have a kidney transplant and the others were ineligible due to co-morbidities. The co-morbidities reported by the clinicians as reasons for ineligibility included: visceral Kaposi sarcoma; progressive multifocal leukoencephalopathy (PML); cervical cancer; lymphoma; ischaemic heart disease; liver disease; blindness; systemic unwell; sclerosing peritonitis; amyloid, pulmonary embolism, seizures and hepatitis C co-infection; and peripheral vascular disease. On 31/12/2012, 13 of the ineligible patients were still alive and 6 were transferred or lost to follow-up.

Use of kidney transplantation as a treatment modality for HIV/ESKD patients

Over the 7 year study period (01/01/2005 to 31/12/2012) there was an increasing uptake of KT as a treatment modality for ESKD in HIV infected patients, (see **Figure 1**). Since January 2005, there was a 12 fold increase in the number of transplanted HIV/ESKD patients by December 2012 respectively, N=2 and N=24. The proportion of patients transplanted in relation to the total number of ESKD patients in 2005 was 5% (2/39) vs 31% (24/77) in 2012 (Z score p=0.0015). There was an increase in the number of HIV/ESKD cases that were suitable for KT throughout the study period, (range N= 19 to 35). Of the 69 ESKD cases that were suitable for KT, 34 (49%) had received a kidney allograft. The overall median follow-up time was 25.2 (IQR 12.8, 56.9) months.

Figure 12: Number of patients under follow-up with ESKD, suitable for kidney transplantation, and having received a kidney transplant, stratified by calendar year



Graph representing the number of ESKD patients alive on 31st December of each year is shown by the black bars; the number of patients who are pre-KT and post-KT are shown by the white and grey bars respectively.

Table 12: Characteristics of patients according to ESKD treatment modality over follow-up

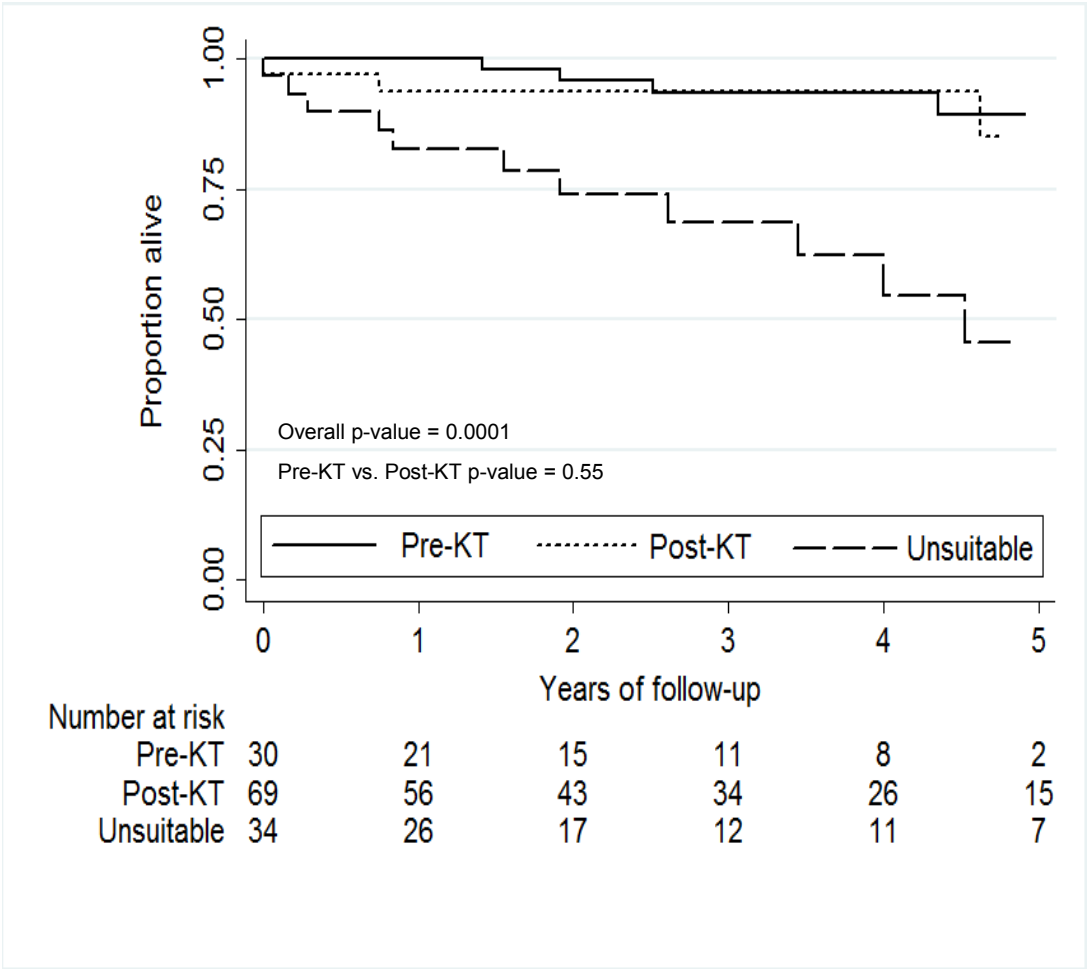
Characteristic		**Pre-KT**	**Post-KT**	**Unsuitable for KT**
		at becoming eligible for KT	**at KT**	**at initiation of pRRT**
N		69^	34	30^
Age, median (IQR)	years	45 (37, 49)	42 (37, 50)	36 (41, 44)
Gender, n (%)	male	48 (70.6)	21 (61.8)	17 (58.6)
Ethnicity, n (%)	black	49 (72.1)	24 (70.6)	19 (65.5)
Time since HIV diagnosis, median (IQR)	years	4.2 (1.5, 8.0)	7.6 (6.6, 10.7)	4.5 (2.4, 8.0)
AIDS (CDC-C), n (%)		23 (33.8)	13 (38.2)	11 (37.9)
CD4 nadir, median (IQR)	cells/mm^3	110 (42, 180)	122 (38, 167)	86 (11, 198)
CD4 count, median (IQR)	cells/mm^3	328 (182, 530)	382 (288, 527)	24 (82.8)
Viral load, median (IQR)	log_{10} copies/ml	1.7 (1.6, 1.7)	1.6 (1.6, 1.7)	3.6 (1.7, 4.9)
eGFR, median (IQR)	ml/min/1.73m^2	8 (6, 12)	6 (5, 8)	7 (5, 15)
Antiretroviral therapy, n (%)	yes	64 (94.1)	34 (100.0)	26 (89.7)
Hepatitis B surface antigen positive, n (%)		4 (5.9)	2 (5.9)	3 (10.3)
Hepatitis C antibody positive, n (%)		2 (2.9)	1 (2.9)	4 (13.8)

^ incomplete data for n=1 patient
KT = kidney transplantation; pRRT = permanent renal replacement therapy; the pre-KT group comprises patients awaiting KT and including those who received a KT during the study period; the post-KT group comprises patients who received a KT

Survival of HIV/ESKD Patients by Treatment Modality

Survival was calculated for three different groups i.e. HIV/EKSD individuals (N=117) pre-KT, post-KT and those unsuitable for KT. The ESKD cases that had received a kidney allograft contributed time to both pre-KT and post-KT survival analyses. The overall median waiting time of those suitable for KT (N=69) since meeting the KT criteria for suitability was 38.6 (IQR 17.1, 54.7) months. By December 2012, those suitable for KT that were being worked up for or awaiting KT had been followed up for a median of 35.8 (15.0, 66.9) months from the date of becoming suitable for KT. **Figure 13** shows patient survival for the pre-KT and post-KT patients and for those who were unsuitable for KT. Survival pre-KT and post-KT was similar (Kaplan-Meier estimates of 100% and 94% at one year, and 89% and 85% at five years, respectively, p=0.53). Survival for patients ineligible for KT was significantly worse (83% at one year and 46% and five years, P<0.0001).

Figure 13: Kaplan-Meier plots showing survival of patients with ESKD, stratified by a) pre-KT, b) post-KT, and c) unsuitable for KT.



Kaplan–Meier survival estimates for patients stratified by KT status. Follow up was measured in years from the date patients became suitable for KT (pre-KT), received their first kidney allograft (post-KT), or initiated permanent renal replacement therapy (unsuitable). Patients who underwent KT could contribute time to both the pre-KT and post-KT cohorts.

Antiretroviral Drug Regimen for HIV/ESKD Awaiting KT

A cross-sectional review of the cART regimens of the 69 patients with ESKD who were suitable for KT (pre- or post-KT) found that 38 (55%) were on a protease inhibitor (PI) and 31 on non-PI (non-nucleoside/tide reverse transcriptase inhibitor [NNRTI], nucleoside/tide reverse transcriptase inhibitor [NRTI] and/or integrase strand transfer inhibitor [INSTI]) containing cART at the most recent clinic visit. Lamivudine and abacavir were the commonest prescribed NRTI (in 74% and 51%, respectively), and darunavir and lopinavir the commonest prescribed PI (in 33% and 18%, respectively). Due to the known risk of ART-associated kidney disease particularly with tenofovir and atazanavir exposure (Hamzah et al., 2015a), I performed a cross-sectional descriptive analysis. Tenofovir and atazanavir were included in the cART regimen of 11 (16%) and 4 (6%) patients respectively.

Estimation of HIV/KT Patients in the United Kingdom

The national estimate of HIV/ESKD patients on 31st December 2012 as previously discussed is 289. Of the 117 HIV/ESKD patients identified in the UK-CHIC cohort there were 42 HIV kidney transplant recipients excluding 10 patients transplanted pre-2005. We would therefore anticipate 103 HIV/KT recipients transplanted between 2005 and 31st December 2012. Data from the Organ Donation and Transplantation reported 17,045 patients that were transplanted in the UK during the 7 year period. Based on this information, the prevalence of HIV infected kidney transplanted recipients is estimated at 0.6%.

2.4. Discussion

Kidney disease is an important co-morbidity in HIV infection. This chapter focused on ESKD in the HIV infected population using a large multicentre study cohort, UK CHIC. To summarise the findings, HIV associated nephropathy was the commonest cause of ESKD representing almost half of all cases with majority being patients of black ethnicity. The overall prevalence of ESKD was low (0.4%) although, a steady increase was observed among black patients while other ethnic groups remained stable. Despite the widespread availability of ART and despite guidelines recommending earlier HIV diagnosis and earlier ART (Asboe et al., 2012), the incidence rate of ESKD did not decline over the study period. Black patients in particular saw a 4 to 5 fold higher ESKD incidence rate compared to other ethnic groups (1.14 [95% CI 0.81, 1.47] vs. 0.24 [0.16, 0.32] per 1000 person years (PY) for black vs. other ethnic patients). Since 2005, kidney transplantation was increasingly used as a treatment modality for HIV/ESKD patients with one third having received a kidney allograft by the end of the study period and another one third awaiting KT. Excellent survival rates were observed for HIV/ESKD patients that were suitable for KT, 100% at one year and 89% at five years.Survival rates of HIV/ESKD patients were similar for both dialysis and kidney transplantation treatment modalities, 89% and 85% at five years, respectively.

In the UK, the prevalence of ESKD in HIV infected individuals was estimated at 0.31% (Bansi et al., 2009). The present study demonstrated that the prevalence of ESKD has continued to increase among HIV positive patients of black ethnicity in recent years, and that the incidence of ESKD has not declined despite widespread use of cART. Since 2005, KT is increasingly used to

manage ESKD, with one third of patients having received a kidney allograft and one third of patients being prepared for or awaiting KT. Excellent survival rates were observed for patients with ESKD who were suitable for KT even if they were maintained on long term dialysis, 100% at one year and 89% at five years.

The prevalence of ESKD among HIV infected individuals in the UK has increased 20-fold from 0.07% in 1998 (Bansi et al., 2009) to 1.35% in 2011. This is reflective of the growing HIV population and decline in HIV-related deaths owing to the use of effective antiretroviral therapy (PHE, 2015a). The overall prevalence in the current dataset (0.4%) although low, is comparable to the 0.36-0.64% reported from other European countries (Trullas et al., 2008, Mazuecos et al., 2012, Bickel et al., 2013, Ryom et al., 2013a, Rasch et al., 2014). North America by comparison has a somewhat higher HIV/ESKD prevalence estimated between 0.75 – 1.65% (Jotwani et al., 2012, Abraham et al., 2015). This may be due to the higher proportion of HIV-infected African American that tend to exhibit higher HIV viral loads, have low ART coverage and often present with advanced HIV disease compared to than other ethnic groups (Lemly et al., 2009). Whereas in the United Kingdom, there has been a decline in the rates of late HIV diagnoses - from 58% in 2003 to 40% in 2014 (PHE, 2015a). Across Europe, the late diagnosis of HIV infected individuals is a persistent issue. In 2014, almost two thirds of newly diagnosed HIV infected were diagnosed with AIDS defining illnesses (WHO, 2015a).

In the current dataset, the incidence rate of HIV/ESKD overall was low 0.7 per 1000PY. When stratified by ethnicities, both black and other ethnic groups failed to demonstrate a decline in the incidence of HIV/ESKD despite the widespread availability of cART (respectively, 2000 to 2001 1.31 vs. 0.29 per 1000PY and 2010 to 2011 1.12 vs. 0.23 per 1000PY). However, the incidence remained up

to 13 fold higher in the black compared to the other ethnic groups over the study period. Data from a large HIV cohort in North America (n=38, 354) demonstrated a modest decline in the incidence rate of black patients from 0.532 to 0.303 per 1000PY and a modest increase in those of non-black patients from, and 0.138 to 0.34 per 1000PY (Abraham et al., 2015). Another study including HIV infected US Veterans (n=22,156) the crude estimate of ESKD was 3 per 1000PY (Jotwani et al., 2012). This is almost a 4 fold difference in the incidence rates among black ethnic patients between the UK and North America. This observation may be due to the differences in antiretroviral prescribing practices where around 2010 the UK had a more conservative approach to initiating cART (CD4 counts < 200 cells/mm^3 (Nelson et al., 2011)) compared to the USA that offered wider access (CD counts 350 to 500 cells/mm^3 (DHHS, 2010)). Furthermore, the eGFR definition of ESKD is estimated much higher i.e. <30 mL/min/1.73m^2 (Abraham et al., 2015).

Factors associated with developing ESKD in the present cohort were black ethnicity, older age, lower CD4 cell count and hepatitis B/C co-infection. In an earlier UK study, multivariable analyses found only black ethnicity and lower CD4 cell count to be associated with ESKD (Bansi et al., 2009). Other observational cohort observed similar factors in addition to traditional factors, diabetes, hypertension, cardiovascular disease, hypoalbuminemia and proteinuria and IVDU (Jotwani et al., 2012, Bickel et al., 2013, Ryom et al., 2013a, Mallipattu et al., 2014, Ryom et al., 2014).

With the decline in presentation of patients with advanced HIV disease, the occurrence of HIVAN has decreased and as a consequence reduced the number of HIV/ESKD cases (Wyatt and Klotman, 2007). In the UK, the proportion of patients presenting with advanced HIV disease i.e. severely

immunocompromised at diagnosis with a CD4 count <200 cells/mm^3 was 30% in 2009 and 28% in 2012 (HPA, 2012). In our cohort the proportion of HIVAN cases has decreased from 52.9% (36/68) in 2007 (Bansi et al., 2009) to 46% (54/115) cases in 2012. Overall, HIVAN is the most common form of CKD in HIV infected and those of African descent (Gerntholtz et al., 2006). Following HIVAN diagnosis, progression to ESKD often occurs within months (Weiner et al., 2003). Based on this together with reduced access to cART of those eligible (35.8% of 21.2 million) (UNAIDS, 2015) it is probable that there is a high prevalence of HIV/ESKD in sub-Saharan Africa. HIVAN is the third leading cause of kidney disease among patients of black ethnicity in high income countries (USRDS, 1999, Gerntholtz et al., 2006). The risk of establishing ESKD among African-Americans was 16.2 fold higher in HIV infected patients compared to 6.7 fold in uninfected patients (Lucas et al., 2007). The incidence of ESKD in a cohort of US veterans was 7.3 fold higher among black patients with HIV compared to age and gender matched white participants (Choi et al., 2007a). In another cohort (n=4259), African-Americans with CKD were found to be 9 times more at risk of progressing to ESKD than Caucasian patients (hazard ratio 1.9 and 17.7 respectively) (Lucas et al., 2008). It has been thought that the increased risk of ESKD among the black patients could possibly be as a consequence of predisposing genetic polymorphisms (Kiryluk et al., 2007, Estrella et al., 2015).The susceptibility of black patients to develop HIVAN and FSGS has been linked to polymorphisms of the apolipoprotein L-1 (APOL1) gene which are present in 35% of African and African-American patients (Kopp et al., 2011). Black ethnicity is also a risk factor for immune complex kidney disease in HIV positive patients (Foy et al., 2013), and for diabetes and hypertension in the general population (Norris and Agodoa, 2005).

The current dataset reflects the ageing HIV population in the UK. By 2012, about a quarter of people living with HIV in the UK were over the age of 50 (Beer, 2014). In the general population there is a 1 in 40 for men and 1 in 60 for women lifetime risk of developing ESKD past middle age (Turin et al., 2012). In individuals with reduced kidney function (eGFR 44 – 59ml/min per 1.73 m^2), the risk of ESKD is considerably higher (estimated 1 in 10 for men, 1 in 30 for women). With longer survival in the HIV population there are other competing risks factors that were not investigated in the current cohort. Diabetes and hypertension are the most common cause of ESRD in the wider population (28% in the UK (UKRR, 2012) and 70% in the US (USRDS, 2011)). The additive effect of HIV could also worsen the prognosis of diabetic or hypertensive nephropathy (Bostrom and Freedman, 2010, Mallipattu et al., 2013). Furthermore, chronic use of antiretroviral drug therapy has been found to be associated with the development diabetes and hypertension (Mocroft et al., 2010).

Hepatitis C affects between 240 to 350 million and chronic hepatitis B 375 million people worldwide (Mohd Hanafiah et al., 2013) (Zhang and Hu, 2015). An estimated 9% of HIV individuals in the UK are co-infected with hepatitis C (NAT, 2012). HIV-HCV and HBV co-infection have been associated with developing CKD and progression to ESKD in several studies (Tsui et al., 2007, Izzedine et al., 2009b, Tsui et al., 2009, Fischer et al., 2010, Mocroft et al., 2012, Peters et al., 2012, Lucas et al., 2013, Mohan et al., 2013).

The management of ESKD has evolved over the years. The present dataset shows an increasing uptake of kidney transplantation as a treatment modality

for HIV/ESKD. Sustained suppression of HIV replication and immune restoration in patients who adhere to cART has allowed successful use of KT in carefully selected patients with ESKD (Stock et al., 2010a, Gathogo et al., 2014). Typically, these patients had CD4 cell counts >200cells/mm^3, undetectable HIV RNA levels, and free of opportunistic disease, malignancy, and severe vascular or hepatic co-morbidities. The outcomes of KT in HIV infection are favourable in terms of patient and graft survival albeit high rates of allograft rejection (31 – 44%) (Stock et al., 2010a, Gathogo et al., 2014). An in depth analysis on the outcomes of kidney transplantation in HIV disease are discussed in Chapter 3. In the present analysis uncontrolled viraemia was the main reason that prevented HIV+ patients from receiving a kidney allograft. The survival at one and five years was significantly worse among those ineligible for KT compared to those eligible (83% and 46% vs 94-100% and 85-89% respectively, $p<0.0001$). In the general population, older age, primary renal diagnosis of hypertension and diabetes, race and lower income are several factors associated with extended waiting times for KT (Schold et al., 2011).

In the pre-HAART era, patient survival on dialysis was poor. Before 1995, the survival rate of HIV/ESKD on chronic dialysis ranged between 1.2 – 12 months (Rodriguez et al., 2003). The use of cART may have explained the survival benefit of those on pRRT in the present cohort. An observational study in the US reported one year survival rates of 54 to 74% and 2 year survival of 30% of HIV/ESKD patients on dialysis (Ahuja et al., 2002, Rodriguez et al., 2003). In a French cohort of HIV/ESKD patients on chronic dialysis demonstrated a 1, 2 year survival respectively of 93.8% and 89.4% (Tourret et al., 2006). Other factors known to impact survival of HIV infected patients on pRRT include CD4 count, IVDU and hepatitis C co-infection. In a multivariate analysis, a higher

CD4 count was protective (hazard ratio (95CI), 0.86 (0.80, 0.93) per 50 cells/mm^3 increase) (Ahuja et al., 2003, Rodriguez et al., 2003, Soleymanian et al., 2006). There is a low prevalence of IVDU users in the UK and (NAT, 2013). The poor uptake of HAART observed among HIV-HCV co-infected patients may increase their risk of mortality (Hsu et al., 2001).

The survival of HIV/ESKD by treatment modality (dialysis vs KT) in the current cohort was similar (100% and 94% at one year, and 89% and 85% at five years, respectively, p=0.53). This finding was somewhat similar to another prospective study in Spain with survival rates of those on the waiting list (n=7) compared to those that had received an allograft (n=11) was 72% vs 100% respectively, logrank p=0.089 (Martina et al., 2011).

The excellent survival rates of HIV infected patients on dialysis could be a reflection on the improved HIV and renal care. The high levels of medication adherence in HIV infected individuals could also explain effective management in the HIV/ESKD cohort. Studies have demonstrated that 95% level of adherence of HAART is associated with poor virological and immunological response (Fischl M, 2000, Paterson et al., 2000, Mannheimer et al., 2002, Poppa et al., 2004). This level of adherence is substantially higher compared with other chronic illnesses where 50% adherence has been estimated (Marinker, 1997). Despite excellent outcomes with dialysis as a treatment modality for HIV/ESKD patients, other studies have shown the risk of mortality with prolonged dialysis use. In a transplant registry study over an 11 year study period (2001 – 2012) found an increase in mortality risk was demonstrated among those with longer waiting times (Locke, 2015). The mortality rate ranged from 0 to 30.5 per 100PY for waiting times between 0.8 to 6.1 years. There has been concern that underexposure and inadequate dose adjustment of

antiretroviral drugs with renal insufficiency. A study of HIV infected patients with chronic kidney disease demonstrated that HAART exposure was 14%, 24%, 64% and 49% less respectively for patients with eGFR 30 – 59, 15 – 29, <15 ml/min/1.72m^2 and those on chronic dialysis (Choi et al., 2007b). An associated risk of mortality with inadequate HAART dose adjustment was estimated at hazard ratio, 1.77; 95%CI, 1.27 – 2.46).

The strengths of this study the use of a large HIV cohort, the long study period (12 years) and the use of local HIV and renal databases for case ascertainment. Other key strengths include the near complete dataset with only less than one tenth of all UK CHIC patients missing creatinine data. Regardless of these strengths, there are several study limitations. There may have been residual ascertainment bias because of incomplete creatinine data for UK CHIC patients or incomplete recording of HIV-positive diagnoses on renal databases. The proportion of black ethnic excluded from the analyses is substantially higher than other ethnic groups, 18% vs 6% respectively. Furthermore, some patients had died prior to cohort entry, were lost to follow-up or had dialysed less than three months. This meant that the incidence and prevalence of ESKD estimates may be have been affected. Finally, there may have been some confounding introduced by not including other comorbidities as competing risks e.g. diabetes, hypertension or cardiovascular disease.

2.5. Conclusions

Over a 12 year study period there was an increasing number of HIV infected individuals with ESKD. By the end of the study period, approxiamtely half of those eligible for KT had received an allograft. The lack of HIV virological control was the primary reason that prevented KT in HIV infected patients. There were similar five-year survival rates for transplanted patients and those awaiting KT. Despite demonstrating no survival benefit of KT compared to dialysis, other benefits of KT were not measured in the current analysis e.g. quality of life measures, cardiovascular co-morbidities and health economics warrant further study.

Chapter 3. HIV Kidney Transplantation

3.1. Introduction

The previous chapter identifies the increasing need for kidney transplantation in HIV infected patients with end-stage kidney disease. With the increased patient survival following kidney transplantion this chapter looks to determine the feasibility of kidney transplantation in HIV infected individuals. Prior to 2010 there was a paucity of data on the safety and efficacy of HIV kidney transplantation. In the transplant setting, HIV infection was also considered an absolute contraindication (Spital, 1998, EBPG, 2000, Bhagani et al., 2006). This was especially in the pre- and early HAART era when HIV disease was associated with a poor life expectancy. This was propagated by concerns of using immunosuppressive agents that could precipitate opportunistic infections or accelerate HIV disease. The advent of highly effective antiretroviral therapy dramatically improved the prognosis of HIV infected individuals (Ahuja et al., 2000, Holkova et al., 2001, Garcia de Olalla et al., 2002, Hoffmann et al., 2004). HIV viral suppression, immune restoration and fewer opportunistic illnesses allowed for more stringent solid organ transplant criteria (Stock et al., 2001, Roland et al., 2003b, Roland and Stock, 2003). Subsequent published reports were able to demonstrate comparable patient survival rates among HIV infected transplant recipients compared to their HIV negative counterparts (Erice et al., 1991, Ahuja et al., 2000, Roland et al., 2003a, Stock et al., 2003b, Toso et al., 2003b, Abbott et al., 2004, Tan et al., 2004b, Bhagani et al., 2006). However, despite the positive findings there was still reluctance in the transplant community to consider HIV infected individuals for transplantation. A USA transplant survey showed 5 to 9 % in favour of HIV transplantation (Spital, 1998, EBPG, 2000).

In 2005 guidelines were developed in the UK to advise clinicians on kidney transplantation in HIV infected patients (Bhagani et al., 2006). The guidelines HIV specific inclusion and exclusion criteria summarised in **Table 13**, **Table 14** and **Table 15**. The transplant criteria focused on HIV virological control, immune status, prior history or existing opportunistic infections and malignancies. The guidelines also recommended living donor transplantation rather than cadaveric donation. Where living donation was considered, it was advised that the donors be informed that "*…HIV kidney transplantation was an 'experimental' or 'new' procedure and that the prognosis for graft and patient survival was considered significantly less than average."(Bhagani et al., 2006)*.

Table 13: HIV Disease Specific Kidney Transplantation Inclusion Criteria

HIV Disease Specific Inclusion Criteria (Bhagani et al., 2006)
▪ CD4 > 200 cells/microlitre for at least six months ▪ Undetectable HIV viraemia (< 50 copies/ml) for at least 6 months ▪ Demonstrable adherence and a stable HAART regimen for 6 months ▪ Absence of AIDS defining illness following successful immune reconstitution after HAART ▪ Available anti-retroviral treatment options in the future (this must be discussed and confirmed with the treating HIV physician)

Table 14: HIV Disease Specific Kidney Transplantation Absolute Exclusion Criteria

HIV Specific Absolute Exclusion Criteria (Bhagani et al., 2006)
▪ Previous or current infections that are at high risk of re-activating with immune suppression: o Aspergillus – infection or colonisation o Any multi-resistant fungal infections o Cytomegalovirus (CMV) disease with any activity and unresponsive to first line therapy o Influenza or RSV infection within 30 days o Active bacterial infections o Mycobacterial infections – unless there is clear evidence of successful treatment ▪ Advanced cardiopulmonary disease ▪ History of neoplasms except solid tumours adequately treated and disease free survival documented for > five years ▪ HTLV-1 positive patients ▪ Patients with significant human papilloma virus (HPV) associated advanced cervical and anal intraepithelial neoplasia (CIN/AIN III) and carcinoma in situ need to be excluded ▪ Hepatic cirrhosis (F4 fibrosis by Metavir if HBV/HCV co-infection) and evidence of active viral replication if HBV/HCV co-infected ▪ Pregnancy ▪ Continuing use of illicit recreational drugs

Table 15: HIV Disease Specific Kidney Transplantation Exclusion Criteria

HIV Disease Specific Exclusion Criteria (Bhagani et al., 2006)
▪ Documented history of progressive multifocal leukoencephalopathy (PML) ▪ Extracutaneous Kaposi's Sarcoma (KS) ▪ EBV and HHV8-related lymphoproliferative disorders (Lymphoma and multicentric Castleman's syndrome) ▪ CD4 count < 200 cells/microliter ▪ Persistent HIV viraemia despite HAART ▪ Continuing non-compliance with anti-retroviral therapy ▪ More than three-class HIV resistance and lack of future HIV treatment options

Concerns of allograft rejection from early reports prompted transplant listing criteria such as HLA DR graft match and avoidance of expanded criteria donors for cadaveric donation. Pre-transplant assessment included vaccinations, cytology screening, cardiovascular and ophthalmology review for active CMV retinitis. There was no strict guidance on post-transplant immunosuppressant management however; the guidelines suggested that consideration be given to the risk of allograft rejection in the HIV infected population. The use of immune depleting agents such as polyclonal (e.g. antithymocyte globulin) or OKT3 antibodies was contraindicated. However, interleukin-2 inhibitory agents (e.g. basiliximab, daclizumab) were permitted. Recommended maintenance immunosuppression was to include calcineurin inhibitor, mycophenolate and tapering glucocorticoids. A four week pre-transplant calcineurin inhibitor and mycophenolate dose finding trial as a strategy to manage drug interactions with certain antiretroviral drugs.

Since the publication of the UK guidelines more than 5 years prior to initiating this study, there was a paucity of data to describe the outcomes of HIV kidney transplantation. Furthermore, there was an increasing demand for transplantation that in the general population improved patient survival and quality of life (Burra and De Bona, 2007, Landreneau et al., 2010, Rambod et al., 2011). The focus of this chapter is to describe the UK experience of kidney transplantation performed in HIV infected patients.

Purpose of study

The main purpose of the UK HIV Kidney Transplant (UK HIV/KT) Study was to evaluate the clinical outcomes of kidney transplantation in HIV positive patients with fully suppressed HIV RNA levels. The specific aims of this study include:

Primary aims

Aim 1: An evaluation of kidney transplantation in HIV disease on patient survival

Hypothesis (H_0) 1.1: Kidney transplantation in HIV-positive patients has comparable patient survival outcomes to the general UK population.

Aim 2: An evaluation of kidney transplantation in HIV disease on allograft survival

Hypothesis (H_0) 1.2: Kidney transplantation in HIV-positive patients has comparable graft survival outcomes to the general UK population.

Aim 3: An evaluation of kidney transplantation in HIV disease on allograft rejection

Hypothesis (H_0) 1.3: Kidney transplantation in HIV-positive patients has associated allograft rejection rates comparable to the general UK population.

Secondary aims

Aim 1: A description of host/donor baseline clinical characteristics as outlined in Table 16**.**

Aim 2: Descriptive analyses of post-transplant allograft function in HIV/KT recipients in the first year of follow-up and at last clinic visit.

Aim 3: Descriptive analyses of HIV management post-transplantation restricted to first year of follow-up and at last clinic visit.

Aim 4: Descriptive analyses of post-transplant immunosuppressant drug therapy management restricted to the first year of follow-up and last clinic visit.

Aim 5: Descriptive analyses of post-transplant management of pharmacokinetic drug interactions between specific antiretroviral and immunosuppressant drug interactions.

Aim 6: A description of post-transplant complications in HIV/KT recipients. Specific complications include opportunistic infections, HIV disease progression, tumours and malignancies.

Aim 7: Descriptive analysis of post-transplant changes in CD4 T cell counts in HIV/KT recipients restricted to first year of follow-up.

3.2. Methods

The UK HIV/KT Study was initiated in 2009 by a steering committee made up of clinicians, statisticians, nurses and pharmacists (**Appendix B**). Data from this study were used for analyses presented in Chapter 3 to 6 of this thesis.

Study Design

This was a national, observational cohort study that included 40 Transplant and referring HIV centres (**Appendix C**).

Ethics Approval

The study was approved in 2009 by a Multicentre Research Ethics Committee (MREC) (reference 09/H1014/36) (**Appendix D**) and local centre NHS Research and Development (R&D) departments.

Funding

No Funding was received to conduct this study.

Patient Enrolment

Case ascertainment was determined by clinicians at the local centres. Clinicians were invited to participate in the study by advertisements placed through specialist clinical networks. Specialist clinical networks included: British HIV Association; HIV Pharmacy Association; British Transplant Society; and the UK Renal Pharmacy Group. Cases were also linked from the UK-CHIC database. Link data used were date of birth, ethnicity and date of transplant.

Local databases and medical records were searched to identify patients coded as having a “positive HIV antibody test” and “kidney transplant”. Clinic lists and clinician recall were also used to identify cases.

Data were used from HIV positive individuals that had a kidney transplant up to 31st December 2013. HIV/KT individuals were enrolled into the study if they met the inclusion criteria.

Inclusion criteria

1. Patients that acquired HIV prior to kidney transplantation
2. Patients ≥ 18 years of age
3. Patients that received a kidney transplant in the United Kingdom

Exclusion criteria

1. HIV+ patients that received a kidney transplant abroad
2. Patients with no available data

Data Collection

A standardised case reporting form (CRF) was designed following discussions with the UK HIV/KT study steering committee (**Appendix E**). The CRF contained information summarised in **Table 16** and **Table 17**. CRFs were completed by the Transplant and HIV centre. Since the CRF contained demographic data to include patient initials, date of birth, ethnicity and gender; it was possible to cross-check for duplication. Each record from each of the centres were checked for missing information and merged into one form. During the merging process where there was conflicting information or inaccuracies, centres were contacted to verify information. Ambiguous or missing information on the final version of the form were also verified by local clinicians. The final 'clean' dataset was then transferred to an electronic database. Data were stored on STATA statistical software database for analyses. Data quality control processes using STATA commands were also performed to identify missing or conflicting data. For example, if the date of the last clinic preceded the date of transplant. Any records that contained ambiguous information were excluded from analysis.

Table 16: Baseline Data Collected in the UK HIV Kidney Transplant Study

Demographics	Date of birth
	Gender
	Ethnicity
	Patient Initials
HIV Background Information	Date of HIV diagnosis
	HIV risk of acquisition
	Baseline HIV viral load
	AIDS diagnoses prior to KT
	Date of AIDS diagnoses prior to KT
	CD4 T cell count nadir prior to KT
	CD4 T cell count at KT
	Antiretroviral drug therapy history prior to KT
	Antiretroviral drug therapy start date
Renal Background Information	Aetiology of kidney disease
	Methods used to confirm kidney disease (e.g. biopsy, radiology, or other)
	If applicable, dialysis history
	Dialysis start date
Co-morbidities & Co-infections	Cardiovascular disease
	Diabetes
	Hypertension
	History of tumors/neoplasms/malignancy
	Hepatitis B surface antigen (HBV DNA if applicable)
	Hepatitis C antibody (HCV RNA if applicable)
	Cytomegalovirus IgG serology
	Other

Table 17: Post-transplant Data Collected in the UK HIV Kidney Transplant Study

Donor Information	Age (if known)
	CMV IgG serology (if known)
	HLA mismatch status
	Allograft type – cadaveric or living donor
	Cold ischaemic time (if known)
	Warm ischaemic time (if known)
	Calculated Reaction Frequency (CRF)
Allograft Outcomes	Date of transplant
	Delayed graft function (if applicable)
	Allograft rejection (if applicable)
	Date of allograft rejection episodes (if applicable)
	Details of allograft rejection treatment
	Details of graft loss (if applicable)
	Histopathology report (s) including protocol biopsies
Post-transplant Laboratory Measurements	Serial CD4 T cell counts
	Serial HIV viral load counts
	Serial serum creatinine measurements
	Serial Immunosuppressant drugconcentrations
	Blood pressure at last clinic visit
	Cytology reports
Post-transplant Medication	cART regimen information
	Immunosuppressant drug therapy information including doses and dosing intervals
	Chemoprophylaxis medications
	Other concomitant medications
Post-transplant Complications	Opportunistic infections and management
	Malignancies / Tumours
Recipient Information	Weight at KT
	Height
	Details on previous transplants (if applicable)
	Details of simultaneous transplants (e.g. SPK or SLK)
	Outcome at last visit (dead/alive/lost to follow-up/transfer of care)
	Cause of death (if applicable)

The UK experience of the first 35 HIV/KT cases identified that had been transplanted up to 31/12/2011 has been published, (see Appendix A). Data analyses of the final dataset are represented in this chapter.

Definitions

Delayed graft function

Delayed graft function was defined as the need for dialysis in the first week post-KT and whose grafts functioned thereafter.

Primary non-graft function

Patients whose grafts never functioned and required maintenance dialysis within 6 months of KT were considered to have primary allograft failure.

Acute rejection

Acute allograft rejection was defined as confirmed histopathological features of rejection requiring the use of enhanced immunosuppression to counter acute deteriorations in graft function within the first year post-KT. This was then referred to as '*biopsy proven acute rejection'* (BPAR). Grading of the severity of acute rejection (e.g. Banff classification (Jennette, 2007)) was not evaluated due to non-standardised grading criteria between centres. Interpretation of the allograft rejection type was derived from histopathology reports as summarised in **Table 18**.

Table 18: Types of Allograft rejection

Hyperacute allograft rejection	*Occurs within minutes or hours post-transplant in pre-sensitised recipients with circulating HLA, ABO or other alloantibody-to-donor endothelial surface antigens (Jennette, 2007).*
Acute cellular rejection	*Develops in the first few weeks post-transplant and declines after the first 3 months. Although, it can still occur at any time when immunosuppressive treatment is inadequate. ACR is T cell mediated usually due to reduced or stopping immunosuppression. ACR is classified into two types. Type I cellular rejection is histologically characterised by at least 25% of interstitial inflammation accompanied with moderate tubulitis. Type II is vascular in nature and is defined by the presence of mononuclear cells beneath the vascular endothelium (McKay and Steinberg, 2010).*
Antibody mediated rejection (also referred to as acute humoral rejection (Mauiyyedi et al., 2002))	*Occurs at any time (days to years) post-transplant. Acute ABMR is defined by four criteria (Racusen et al., 2003, Takemoto et al., 2004, Colvin and Smith, 2005):* *(i) Clinical evidence of acute graft dysfunction* *(ii) Histological evidence of acute tissue injury* *(iii) Immunopathological evidence for the action of antibodies i.e. positive staining for complement component 4d (C4d) deposited in peritubular capillaries or antibodies or C3 in arteries* *(iv) Serological evidence of HLA-specific antibodies or other donor-specific antibodies at the time of biopsy.*

Chronic rejection	*Chronic rejection is characterised by a chronic allograft dysfunction with a slow loss of function accompanied by proteinuria and hypertension. Histopathological findings are defined by fibrointimal thickening of arteries, interstitial fibrosis, tubular atrophy and lesions characteristic for chronic allograft nephropathy (CAN) (Joosten et al., 2005).*

Inconclusive reports or reports of subclinical rejection were referred to local histopathologists and clinicians for interpretation. Information on the presence of polyomavirus (e.g. BK virus) or cytomegalovirus induced nephritis was also collected. Calcineurin inhibitor nephrotoxicity was excluded due to lack of strong evidence to associate systemic blood concentrations of ciclosporin or tacrolimus to CNI induced nephrotoxicity (Naesens et al., 2009).

Steroid resistant rejection

This is defined in literature as rejection that does not result in a decline in creatinine levels within 20% of baseline within 3 to 5 days after the last dose of intravenous methylprednisolone (Shinn et al., 1999, Bock, 2001). In another definition, steroid resistant rejection was considered if alternative treatment (e.g. antithymocyte globulin, IVIG, etc) was used (Bock, 2001). In this study, steroid resistant rejection was defined as rejection that required more than one treatment course of high dose IVMP for the same rejection episode and/or resulted in the use of alternative immunosuppressive therapies (e.g. IVIG or ATG).

Allograft function

Allograft function was expressed as estimated glomerular filtration rate (eGFR) using IDMS-adjusted serum creatinine measurements and chronic kidney disease epidemiological collaboration (CKD-EPI) equations (Pugliese et al., 2011).

New onset of diabetes mellitus (NODAT)

New onset of diabetes mellitus after transplant (NODAT) was defined as impaired glucose tolerance post-transplant requiring treatment with oral hypoglycaemic agents and/or insulin.

Cytomegalovirus reactivation

The management and prevention of cytomegalovirus (CMV) infection varied between centres with valganciclovir prophylaxis administered for three months post-transplantation irrespective of donor/recipient CMV IgG status at some centres, while others prescribed CMV prophylaxis to those with mismatched CMV IgG serology i.e. CMV IgG negative recipient receiving an allograft from CMV IgG positive donors. Post-transplant CMV surveillance was routine for all patients with preemptive valganciclovir treatment if the CMV viral load exceeded 3-4000 copies/mL.

HIV Disease Progression

HIV disease progression was defined as persistent loss of virological control (> 50 copies/ml) at any point post-transplantation with an accompanying AIDS defining illness (Schneider E, 2008, BHIVA et al., 2014). The CD4 T cell count was not taken into account as post-transplant immunosuppressant drug management included agents known to cause lymphocyte depletion.

HIV Viral Load Blips

A virological blip was defined as a detectable VL between 50 - 400 copies/mL, which is preceded and followed by an undetectable result (<50 copies/mL) without any change of antiretroviral therapy (BHIVA et al., 2014).

Statistical analysis

All analyses were performed using Stata (version 12.1 StataCorp, Texas, USA). Baseline parameters were expressed as n (%), mean (SD) or median (IQR). Wilcoxon-ranksum test was used to compare medians; Z-tests were used to compare means; and two-sided chi-squared (X^2) or Fisher's exact test to compare proportions. Patient survival and graft survival were calculated using Kaplan-Meier estimates. Cumulative hazard of first allograft rejection was calculated using Nelson-Aalen estimates. Cox proportional hazard analysis was performed to identify recipient/donor factors associated with allograft rejection.

In order to account for the correlation of between repeated measures data, a multi-level mixed effect linear regression model was performed. The repeated measures data analysed included renal graft function measured at weeks 1, 2, 4, 6, 8, 12, 24, 36, 52 and at last clinic visit. This mixed effect model was performed using unstructured within-subject covariance to examine whether there was a significant difference ($p < 0.05$) in change of graft function from baseline to week 52 and last visit for patients that experienced allograft rejection compared to those that remained rejection free post-transplant. The association of allograft rejection and the slopes of graft function versus time post-transplant were also examined using mixed-effect models allowing for a random intercept and slope. Graft function was expressed as eGFR calculated using the CKDEPI equation. The analysis was performed using the *xtmixed* command in STATA (version 12.0).

3.3. Results

Patient and donor characteristics

97 HIV positive KT recipients were identified; 93 were transplanted in the UK up to 31st December 2013, the remaining four patients had received renal allografts in the USA and Sweden prior to 2005, Belgium and India (see **Figure 14** for full patient disposition). Since 2005, there was a yearly increase in kidney transplantation of HIV positive individuals in the UK, (see **Figure 15**).

Figure 14: Patient disposition for UK HIV/KT cases transplanted up to 2013

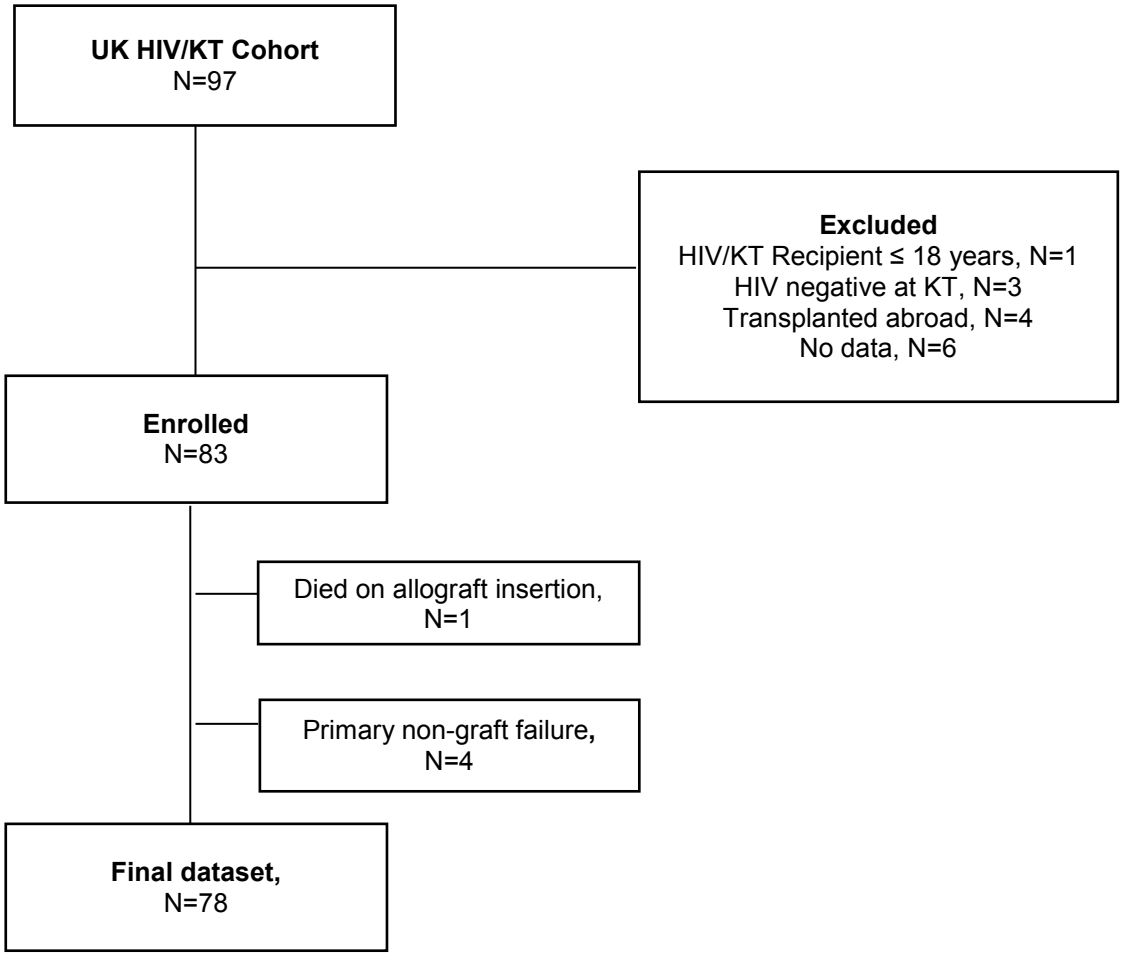
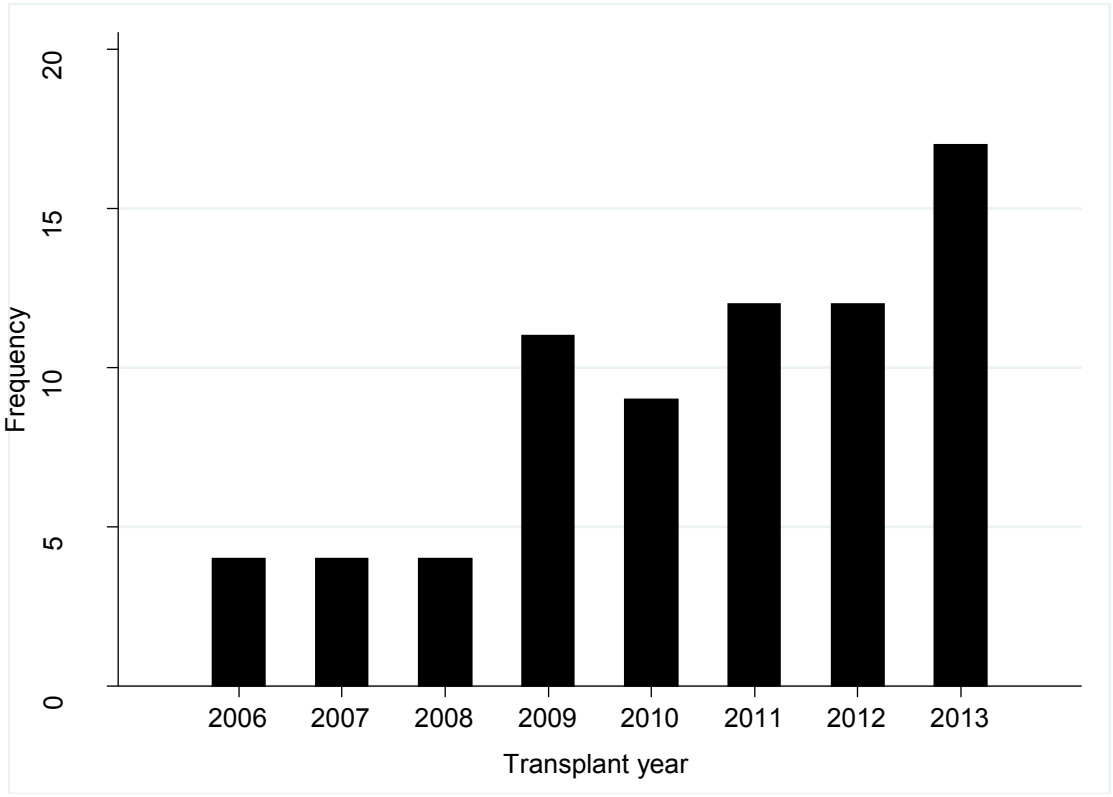


Figure 15: UK HIV/KT by Transplant Year



Graph represents number of HIV kidney transplant recipients stratified by year for period covering up to 2013.

There were 14 patients that did not meet the study criteria and were therefore excluded from further analyses. Of those excluded, there was one child (11 years of age), three adults that acquired HIV post-transplantation, four were transplanted abroad (India, Belgium, USA and Berlin) and the remaining six patients had no data available. The six patients were transplanted at Oxford Radcliffe hospital (n=4), Birmingham (n=1) and Manchester (n=1). All were referrals from external HIV centers (unknown) and received post-transplant follow-up at their base hospitals.

Of those that met the study inclusion criteria (n=83), one patient experienced a fatal cardiac arrest immediately post-KT and 4 had primary non-graft function. In the final dataset (n=78), majority were male (67%) and of black ethnicity (74%) with a history of severe immunodeficiency (**Table 19**). At KT all but one patient had fully suppressed HIV RNA levels. This patient at KT listing, 8 months prior, had a wild type virus being managed with a dual cART regimen (DRV/r plus ETV) and undetectable HIV RNA levels (<40 cps/mL). Clinicians suspected non-adherence as the cause of virological failure (3544 copies/mL). Virological control was achieved post-KT on resuming regular cART regimen. The median nadir CD4 cell count pre-KT was 90 (40, 171) cells/mm^3, and 44% of patients had experienced at least one AIDS defining illness. Of note, two patients had visceral Kaposi sarcoma prior to KT and one patient had active hepatitis C co-infection at the time of KT. HIVAN was the commonest kidney diagnosis (52%), other diagnoses are summarized in **Table 19**. All patients were stable on cART at KT. The median (IQR) CD4 cell count at KT was 366 (277, 516) cells/mm^3; 6 patients (8%) had median (IQR) CD4 cell counts <200 (median 131, range 76-194) cells/mm^3. None of the patients interrupted cART in the peri-operative period; 22 (29%) received a pre-transplant trial of immunosuppressive therapy with concomitant monitoring of calcineurin inhibitor drug concentrations to guide post-KT dosing. The median (IQR) age of the donors was 45 (35, 56) years, 44% of allografts were HLA-DR matched, 27 donors (35%) had a known positive CMV IgG serology and 26 patients (34%) received a kidney from a live donor (**Table 20**). All patients were first time kidney transplant recipients, none were re-transplants,

Table 19: Baseline HIV Kidney Transplant Recipient Characteristics

Characteristic	N=78
Age (years), median (IQR)	45 (38, 51)
Male, N (%)	52 (67)
Black ethnicity, N (%)	57 (74)
Risk HIV acquisition, N (%)*	
Heterosexual	54 (75)
MSM	17 (24)
Time since HIV diagnosis (years), median (IQR)**	8 (7, 11)
AIDS (CDC-C), N (%)ŧ	
Mycobacterial infection	15 (19)
Cytomegalovirus (end-organ)	8 (10)
Kaposi sarcoma	3 (4)
CD4 cell count (cells/mm^3), median (IQR)	
At KTŧ	365 (277, 516)
Nadir pre-KT†	91 (39, 169)
HIV RNA <50 (copies/ml), N (%)	77 (99)
Viral Hepatitis, N (%)	
HBsAg positiveŧ	10 (13)
HCV Ab / HCV RNA positive‡	4 (5)
Time on cART (years), median (IQR)†	7 (4, 10)
Class of drugs in cART regimen, N (%)	
PI-containing cART	30 (38)
PI-sparing cART	48 (62)
Pre-KT Dialysis (HD, PD)¶	65 (92)
Duration (years), median (IQR)	5 (3, 7)

Data available for *n=72; **n=76; ŧn=77; ‡n=75; †n=74; ¶n=71
Abbreviations: MSM, men who have sex with men; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; CDC-C, CDC classification system for HIV-infected adults and adolescents stage C; KT, kidney transplantation; cART, combination antiretroviral therapy; PI, protease inhibitor; HD, haemodialysis; PD, peritoneal dialysis

Table 20: HIV Kidney Transplant - Donor characteristics

	N=78
Donor age (years), median (IQR)*	45 (35, 56)
Donor type, N (%)**	
Living	26 (34)
Altruistic	1 (1)
ABOi	1 (1)
Deceased	51 (66)
HLA matching, N (%)ŧ	
Six-antigen-matched kidney	5 (8)
HLA mismatch, median (IQR) *	3 (2, 3)
HLA-DR matched	27 (44)
Recipient/Donor/CMV IgG status	
CMV mismatch (R-D+), N (%)	4 (5)
CMV mismatch (R-Du), N (%)	2 (3)

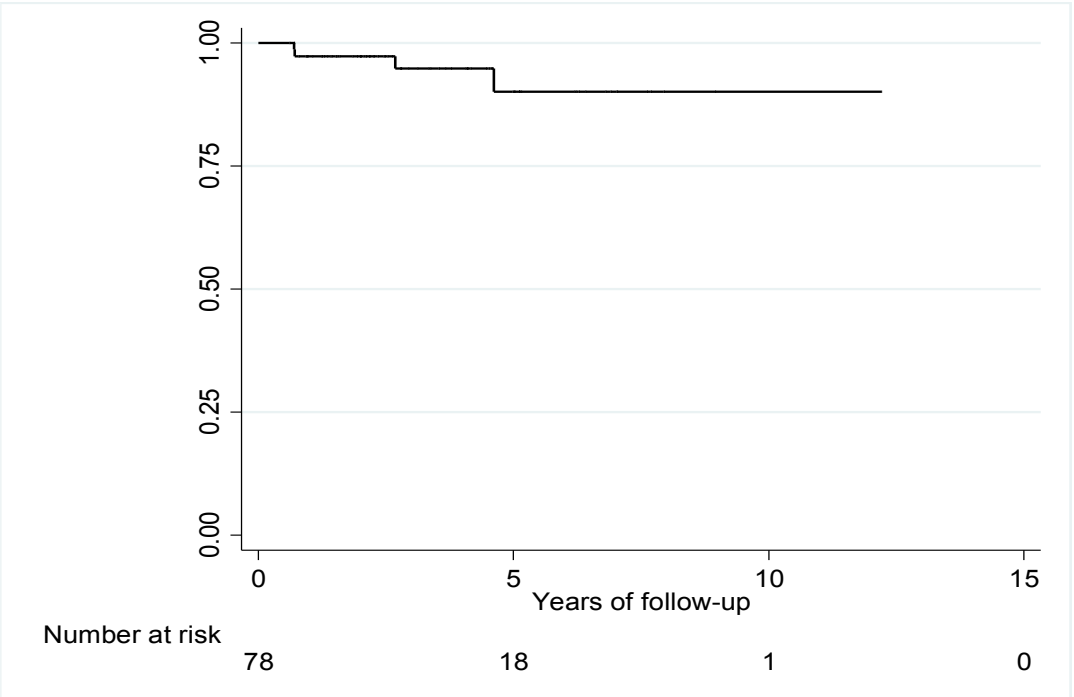
Abbreviations: HLA, human leucocyte antigen; CMV, cytomegalovirus; IgG, immunoglobulin G; R-D+, recipient negative, donor positive; R-Du, recipient negative, donor unknown status; ABOi, ABO incompatible.
* Data available for *n=56; **n=77; ŧn=63

Patient and graft survival

The study participants were followed for a median (IQR) of 31 (19, 55) months, and vital status at 12 months was available for 70. Four additional patients died, three with functioning allografts and one with complete graft failure. Deaths were due to pneumonia seven months after receipt of anti-thymocyte globulin (ATG) as anti-rejection therapy, cardiac failure two years after re-initiation of dialysis, liver failure secondary to hepatitis C and multi-organ failure, microvesicular hepatic steatosis and severe lactic acidosis suspected to be due to drug toxicity. Patient survival at 1, 3 and 5 years post-KT was 97·4%, 94·9% and 90.1% respectively (see **Figure 16a**); the mortality rate was 1.5 (95% CI 0.6, 4.0) per 100 person-years of follow up. Graft survival at 1, 3 and 5 years was 97.4%, 90.2% and 82.3% respectively (see **Figure 16b**).

Figure 16: Patient and Graft Survival after HIV Kidney Transplantation

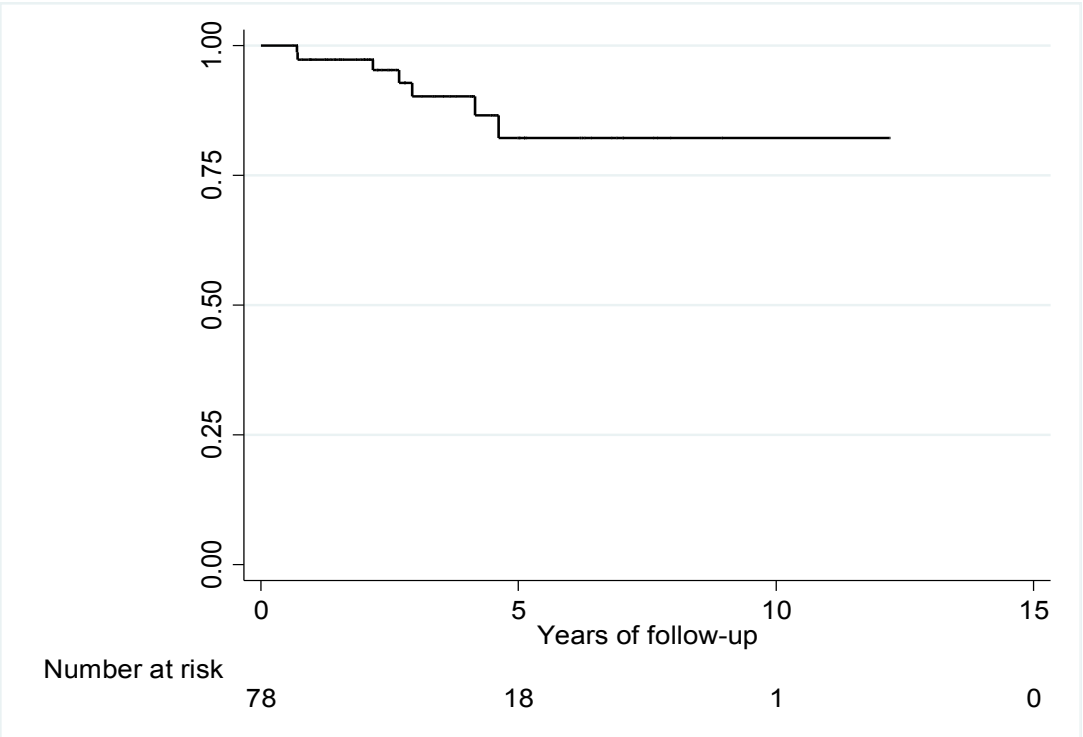
(a) Patient Survival after HIV Kidney Transplantation



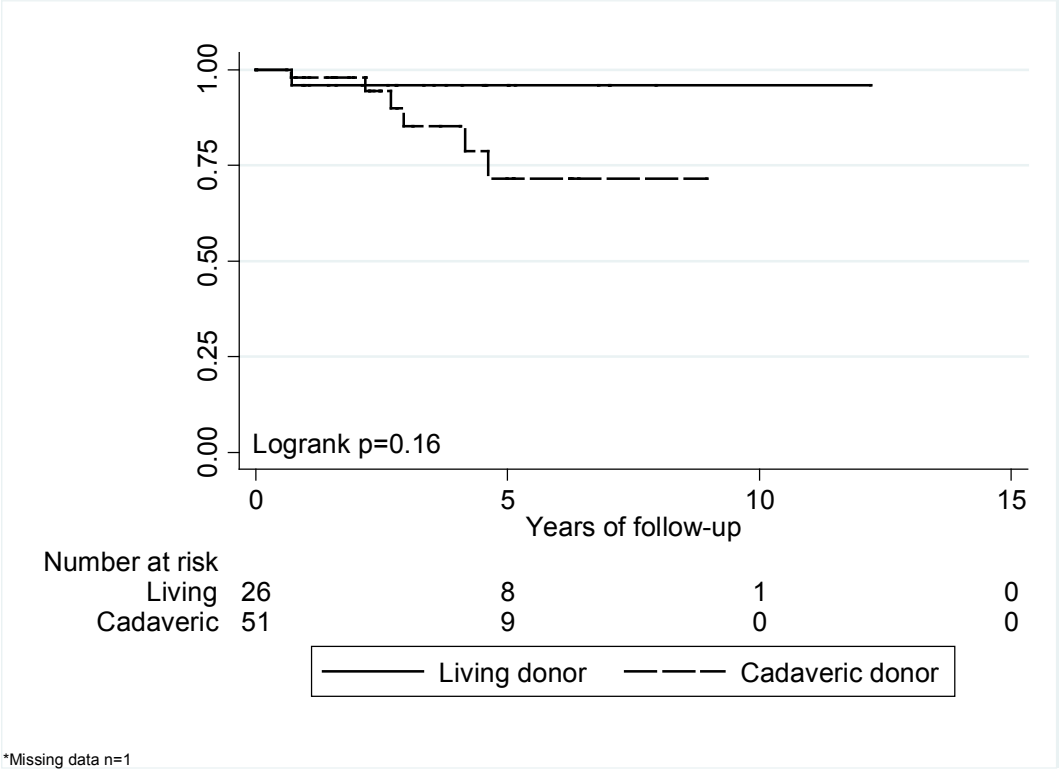
(b) Patient Survival after HIV Kidney Transplantation by Donor Type

*Missing data n=1

(c) Graft Survival after HIV Kidney Transplantation



(d) Graft Survival after HIV Kidney Transplantation by Donor Type



Graph represents Kaplan-Meier estimates of overall patient (a) and graft (d) survival; patient (c) and graft (b) survival stratified by donor type of HIV kidney transplant recipients (n=78) transplanted up to 2013 with follow-up until 31st December 2014. Less than one quarter of patients had 5 years of follow-up.

Post-transplant Immunosuppression

All patients received induction immunosuppressive therapy consisting of high dose corticosteroids (IVMP, intravenous methylprednisolone). Excluding 2 patients that received IVMP only and one ABO incompatible transplant patient, 75 (96%) received additional inductive IS therapies to include monoclonal antibodies – anti-CD25 (basiliximab/daclizumab), n=73 and anti-CD52 (alemtuzumab), n=2. The ABOi transplant received pre-transplant conditioning with anti-CD20 (rituximab) plus plasma exchange. 76 (97%) patients received triple maintenance immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate or azathioprine, and corticosteroid. The remaining two patients were managed with a CNI-minimisation protocol that included induction therapy with alemtuzumab followed by low dose tacrolimus monotherapy (target Tac concentrations 5 to 8 ng/mL). The CNI doses used in the first year post-KT, the CNI concentrations attained, and the relevant target ranges are displayed in **Table 21**.

Table 21: Mean (+/- SD) Calcineurin Inhibitor Doses & Mean (+/-SD) Whole Blood Concentrations in HIV Infected Kidney Transplant Recipients

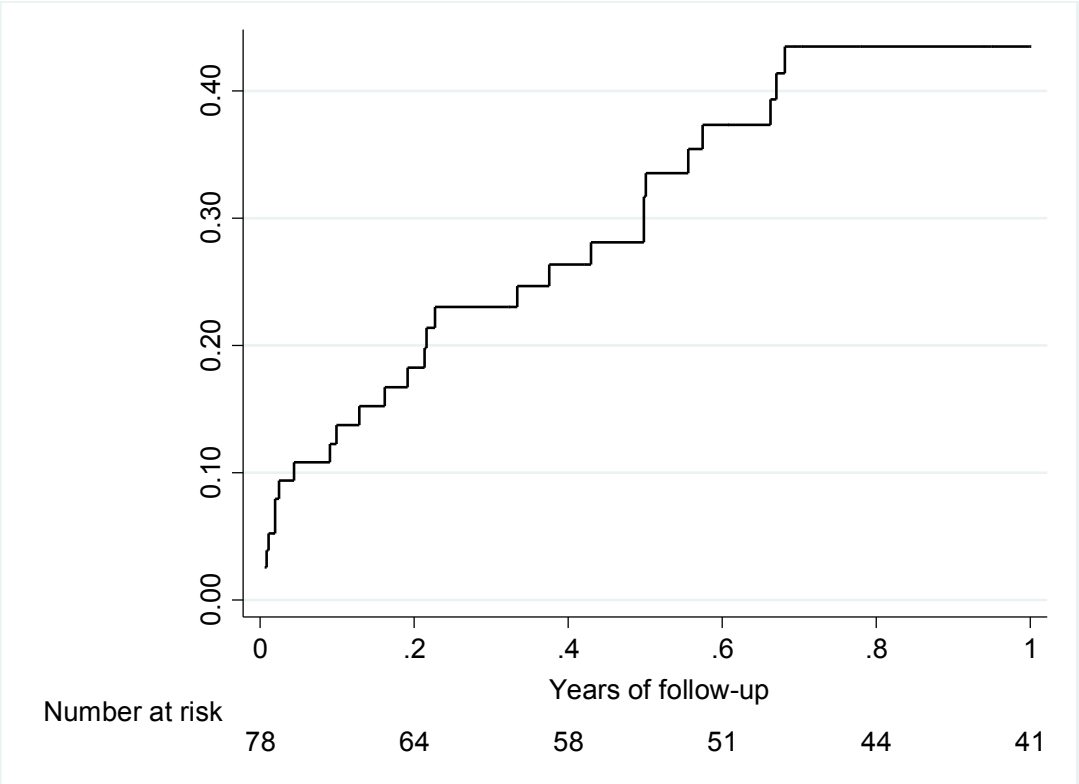
Weeks Post-KT	Ciclosporin					Tacrolimus				
	All patients N=23	PI-containing cART N=14		PI-sparing cART N=9		All patients N=33	PI-containing cART N=9		PI-sparing cART N=24	
	C_t (ng/ml) [b]	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml) [c]	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml)	Dose (mg/kg/day)
1	375±497	496±610	1.3±1.7	184±96	9.6±4.5	9.8±9.1	19.2±13.0[a]	0.0194±0.0225	6.3±2.9[a]	0.13±0.09
2	333±291	402±361	0.8±0.6	233±88	11.0±4.3	10.0±5.9	15.1±8.4[a]	0.0025±0.0017	8.2±3.3[a]	0.18±0.11
4	245±93	237±76	0.7±0.5	259±119	10.6±4.5	12.3±11.2	19.5±21.3[a]	0.0024±0.0034	10.0±3.6[a]	0.24±0.11
6	253±89	255±86	0.5±0.2	250±99	10.2±4.5	10.6±5.6	12.4±9.4[a]	0.0013±0.0006	10.0±3.5[a]	0.024±0.12
8	236±69	224±75	0.4±0.1	260±53	11.6±4.1	9.2±3.2	8.7±4.1	0.0013±0.0010	9.4±2.9	0.22±0.11
12	231±61	238±53	0.4±0.2	217±53	10.7±4.4	9.4±3.6	10.8±5.2	0.0016±0.0020	8.9±2.8	0.20±0.11
24	180±45	186±30	0.4±0.2	171±64	6.6±2.5	9.7±4.1	8.9±4.4	0.0014±0.0013	10.0±4.0	0.18±0.09
36	165±41	167±46	0.4±0.2	163±36	6.5±2.0	8.1±3.3	8.1±4.0	0.0015±0.0013	8.1±3.1	0.18±0.09
52	129±36	142±42	0.4±0.2	119±32	6.4±2.0	9.2±4.4	7.0±1.6	0.0015±0.0015	9.9±4.8	0.14±0.10

[a] P <0.05 (PI-containing cART vs. PI-sparing cART); [b] Target range: 200-350 ng/mL during weeks 1-12, 100 – 250 ng/mL thereafter; [c] Target range: 8-15 ng/mL during weeks 1-12, 5-10 ng/mL thereafter.

Allograft rejection

28 patients (36%) experienced allograft rejection within 12 months of KT. The cumulative hazard (95% CI) of AR in the first year post-KT was 43% (30%, 64%) (see **Figure 17**). The median (IQR) interval between KT and the first AR episode was 2.6 (0.5, 5.9) months. The overall incidence rate of AR during the first year post-KT was 4.3 (95% CI 3.0, 6.2) episodes per 100 person-months, and was similar for patients who received PI-containing vs. PI-sparing cART (5.6 [95% CI 3.3, 9.7] vs. 3.5 [2.1, 5.9] per 100 person-months; p=0·10) and for those who received tacrolimus vs. ciclosporin-based maintenance immunosuppressive therapy at KT (2.2 [1.2, 4.1] vs. 9.1 [5.7, 14.4] per 100 person-months; p=0·0001). Factors associated with the first AR episode in the first 12 months post-KT are described in Chapter 4. 24 patients received pulsed corticosteroids; other or additional treatment interventions to combat AR included intravenous immunoglobulin (IVIG, n=7), plasma exchange (n=6), anti-thymocyte globulin (ATG, n=4), rituximab (n=1), switching CNI choice (n=11, CsA to Tac switch), and augmentation of baseline immunosuppression (n=8).

Figure 17: Allograft Rejection in HIV Kidney Transplant Recipients

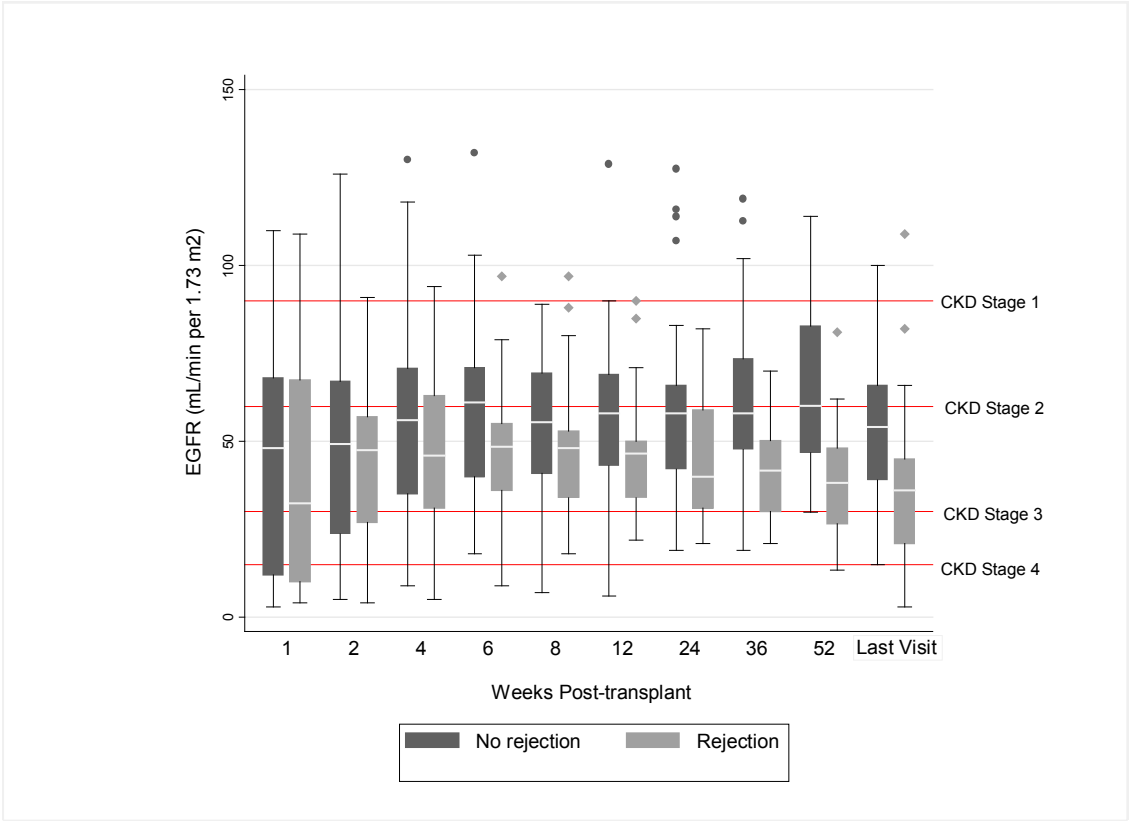


Graph representing Nelson-Aalen cumulative hazard of first acute allograft rejection episode at year 1 post-transplantation.

Allograft function

Primary non-graft function occurred in 4 patients (5%); 3 received an allograft from a deceased donor and 1 from a living donor. Delayed graft function was encountered in 16 patients (21%), all of whom had received a kidney from deceased donors. The overall median (IQR) EGFR estimated by CKD-EPI equation at 1 year and at last clinic visit was 51 (34, 73) and 46 (35, 63) ml/min per 1.73 m^2 of body surface area. The overall median (IQR) change in eGFR at 1 year and at last clinic visit compared to value at month 3 post-KT was -5.5 (-16, 7.9) and -4 (-10.5, 9.8) ml/min/1.73m^2 respectively, (p=0.35). There was a significant decline in graft function in those recipients that experienced acute allograft rejection in the first year post-KT compared to those that remained rejection free, (see **Figure 18**). At 1 year and at the last clinic visit respectively, the median (IQR) EGFR was 38 (27, 48) and 36 (21, 45) ml/min per 1.73 m^2 of body surface area for the AR group and 60 (47, 83) and 54 (39, 66) ml/min per 1.73 m^2 of body surface area for those who remained rejection free, (AR vs No AR at 1 year p=0.0002; last clinic visit p=0.0004). At the last clinic visit, there was a significantly higher proportion of patients with an EGFR <30 ml/min per 1.73 m^2 (CKD Stage 4) and <15 ml/min per 1.73 m^2 (CKD Stage 5) in the AR group compared to No AR group, (X^2 36% (n=10) vs 8% (n=4) p=0.002; 14% (n=4) vs 0% (n=0) p=0.006 respectively).

Figure 18: Graft Function Post-Transplantation Stratified By Acute Rejection at 1 Year

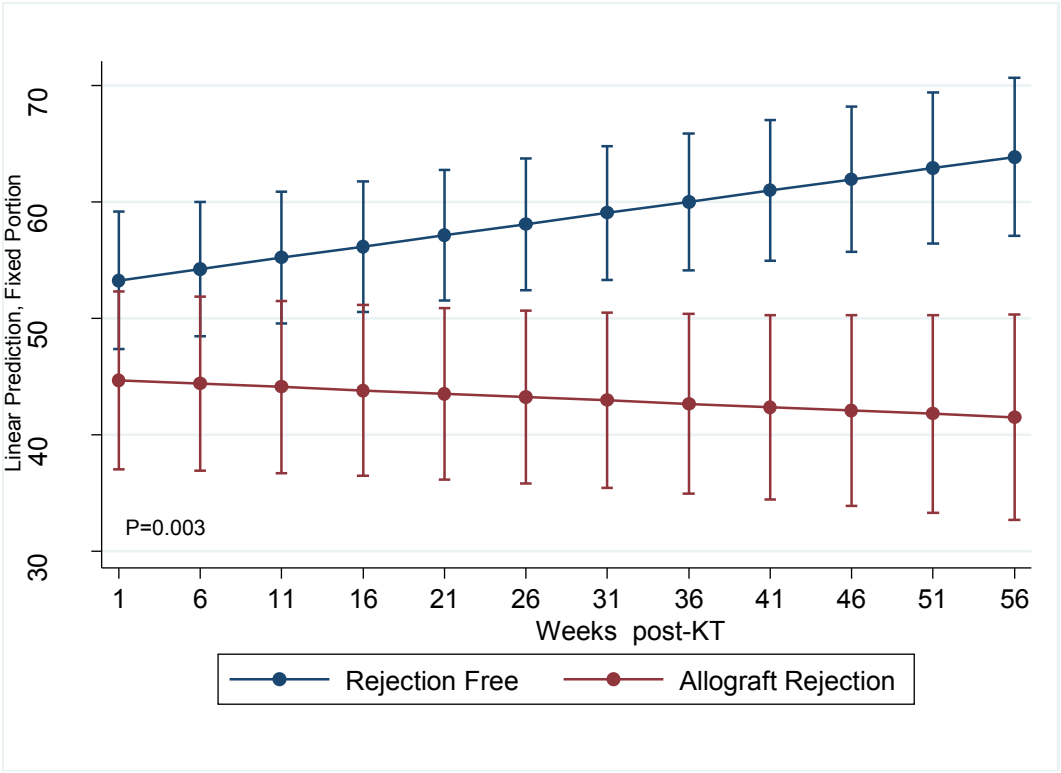


Graph representing changes in graft function, according to acute allograft rejection status at 1 year and at last clinic visit. This is restricted to first AR episode at 1 year. The median (IQR) CKD-EPI EGFR are plotted over time. The red lines represent the staging of chronic kidney disease (CKD).) .

In a multi-level mixed effects model, the eGFR was somewhat lower in those that experienced an allograft rejection over the first year post-transplant compared to those that remained rejection free (-8.3 (95CI -17.9, 1.26) ml/min/1.73^2 lower at baseline, p=0.09). The change in eGFR over the first year post-transplant was significantly different between groups (interaction p=0.003), Figure 19. A slight increase in graft function was observed from baseline to 1 year in the allograft rejection group (+0.19 (95CI +0.09, +0.30) ml/min/1.73^2),

whereas in the rejection free group there was a modest decline in eGFR over time (-0.06 (95CI -0.18, +0.07) ml/min/1.73^2).

Figure 19: Predicted Slopes of estimated Graft Function (eGFR) stratified a priori by Allograft Rejection with 95% CIs



Including eGFR at last clinic visit we similarly observed that At last clinic visit, eGFR was significantly lower in the AR group compared to baseline for those that experienced a rejection episode (-12.7 (95CI -21.8, -3.7) ml/min/1.73^2 lower at baseline, p=0.006). The slopes of eGFR versus time for AR vs AR free groups were similar (interaction p=0.20). Further, both groups demonstrated a somewhat modest decline in eGFR over time, (AR free -0.03 (95CI -0.06, +0.003) vs AR -0.005 (95CI -0.026, 0.016) ml/min/1.73^2).

Post-transplant Complications

HIV Virological Control

Throughout the follow-up period post KT, HIV infection remained fully suppressed in all patients; with transient HIV viraemia (HIV RNA blips 50-139 copies/mL) observed in 6 participants, (See **Table 22**). At baseline, HIVAN was the most common cause of kidney disease (n=4); majority received allografts from deceased donors (n=4) and were taking a PI-containing cART regimen (n=5) and ciclosporin based IS therapy (n=5). Only one recipient did not experience post-KT complications (rejection, infections or tumors/neoplasms). At last clinic visit, patient 1 (see **Table 22**) had nephrotic syndrome which on biopsy showed focal segmental glomerulosclerosis (FSGS) suspected to be secondary to sirolimus, diabetic glomerulosclerosis (although had excellent diabetic control) or HIVAN. Chronic antibody mediated rejection with class 1 donor specific antibodies was suspected in this recipient. A switch to sirolimus had been made 4 years prior when a biopsy revealed chronic allograft nephropathy. All other recipients had an unremarkable review at last clinic visit. Antiretroviral resistance data were not available for any of the recipients.

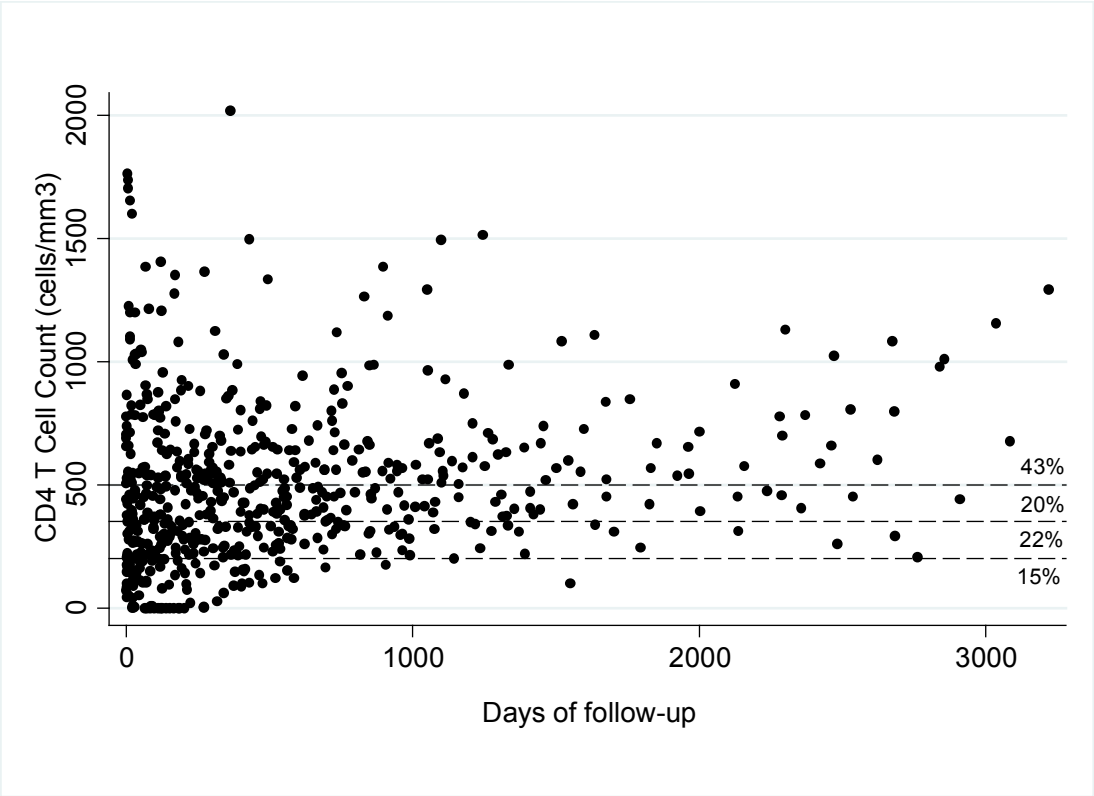
Table 22: Summary of HIV+ Patients that Experienced Viral Load Blips Post-Transplantation

Patient	HIV RNA VL Blip (c/mL)	Day Post-KT of HIV RNA VL Blip	Baseline HIV RNA VL (c/mL)	CD4 Count at KT (cells/mm^3)	CD4 Count at HIV RNA VL Blip (CD4 Count at HIV RNA <50c/mL) (cells/mm^3)	cART at KT	CNI Choice at KT	AR	Post-KT Infections
1	60 80 76 <40	219 222 242 303	180,000	364	467 (240)	ABC/3TC/EFV	CsA	No	Yes (Recurrent UTIs)
2	67 139 101 <50	6 55 218 296	U	457	1352 (562)	FTC/TDF/LPV/RTV	CsA	Yes	Yes (CMV Infection)
3	70 <40	69 73	88,600	566	U (260)	3TC/TDF/DRV/RTV/RAL	CsA	Yes	Yes (Penile HSV)
4	78 <50	391 503	1,249,515	288	453 (332)	ATZ/RTV/3TC/TDF	Tac	No	No
5	80 <40	264 300	750,000	282	538 (U)	ABC/TDF/AZT/LPV/RTV	CsA	Yes	Yes (HSV Encephalitis)
6	111 <50	5 110	14,000	830	830 (720)	ABC/3TC/LPV/RTV	CsA	Yes	Yes (CMV Infection)

AR, allograft rejection; CsA, ciclosporin; ABC, abacavir; 3TC, lamivudine; EFV, efavirenz; FTC, emtracitabine; TDF, tenofovir; LPV/RTV, ritonavir boosted lopinavir; DRV/RTV, ritonavir boosted ritonavir; RAL, Raltegravir; ATZ/RTV, ritonavir boosted atazanavir; AZT, zidovudine; U, unknown; HSV, Herpes simplex virus; CMV, cytomegalovirus; UTIs, urinary tract infections; VL, viral load; c/mL, copies/mL

During the follow-up period, there was overall good immunological status with 43% (n=251) of all available CD4 T cell counts > 500 cells/mm^3, (see **Figure 20**). The overall median (IQR) CD4+ T cell count at 1 year after transplantation was 410 (225, 608) cells/mm^3. The median change of the CD4+ T cell count from baseline to 1 year post-KT was significantly greater for those that received lymphocyte depleting inductive therapies (i.e. alemtuzumab) compared to non-depleting agents (i.e. anti-CD25 monoclonal antibodies) (-296 and -18 cells/mm^3 respectively, p=0.05). Post-transplant nadirs of $\geq$200, 100-199, 50-99 and <50 cells/mm^3 encountered in 63%, 16%, 7% and 11% of patients respectively (n=62).

Figure 20: Post-Transplant CD4 T-Cell Counts



Graph representing all available Post-HIV/KT CD4 T cell Counts from 62 recipients. Proportions represent counts from each category as follows: 43%, >500 cells/mm^3; 20%, 350 – 500 cells/mm^3; 22%, 200 – 350 cells/mm^3; 15%, <200 cells/mm^3.

Opportunistic Infection

The occurrence of opportunistic infections was infrequent (41%, n=29). Post-transplantation, all recipients received chemoprophylaxis against *pneumocysitis jirovecii* (PCP) and 45% (n=32) received CMV prophylaxis. CMV prophylaxis with valganciclovir was administered for 3 months post-KT to recipients with CMV donor/recipient mismatch or unknown IgG serology. All other recipients had CMV surveillance with preemptive therapy. PCP occurred in one patient and CMV in 20 patients (26%); none had extra-renal tissue-invasive CMV disease. Treatment of CMV viraemia included reduction of immunosuppressive therapy, discontinuing mycophenolate or treatment with valganciclovir when CMV PCR > 3000 copies/mL. BK viraemia occurred in 8 patients with 3 patients having histological evidence of BK nephropathy; all patients were managed with reductions in immunosuppressive therapy. Epstein-Barr virus (EBV) was detected in blood of 5 patients although; there was one case of immunodeficiency associated EBV positive lymphoproliferative disorder of diffuse large B-cell lymphoma (DLBCL) subtype confirmed on biopsy 4 years post-KT. This patient having waited 8 years on haemodialysis for a kidney transplant, experienced severe central nervous system CMV and HSV reactivation with associated encephalitis 8 months post-KT. This was resolved with valganciclovir treatment and switching the choice of calcineurin inhibitor from ciclosporin to tacrolimus and the addition of maraviroc to his antiretroviral therapy combination (abacavir, tenofovir, lopinavir/ritonavir). A further 3 years after, a biopsy histology of the colon showed features of immunodeficiency associated EBV positive lymphoproliferative disorder (DLBCL).

The patient's DLBCL was managed with 4 cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and a few doses of rituximab monotherapy. At the last clinic visit (01/2016), the patient had lost his graft and returned to maintenance haemodialysis.

Herpes simplex virus infection occurred in 5 patients; 4 had genital HSV treated with aciclovir. One case of HSV encephalitis that required critical care management, treatment with aciclovir and the addition of maraviroc to cART regimen (abacavir/tenofovir/lopinavir/ritonavir). One patient developed oesophageal candidosis treated with an antifungal.

There were two cases of Kaposi Sarcoma (KS). The first case of cutaneous KS managed with docetaxel and a change in immunosuppressive therapy from tacrolimus to sirolimus, resulting in complete resolution. The second case was of KS lesions on the dorsal of left and right foot that was human herpesvirus type 8 (HHV8) positive; treatment included inclusion of sirolimus, active monitoring and consideration for radiotherapy if lesion was progressive.

Tumors/Neoplasms

Apart from the two cases of KS and the case of PLTD, there were four tumors/neoplasms reported. Two cases were of Bowen's disease, one basal cell carcinoma and one lentiginous junctional melanoma. Treatment for all cases involved surgical excision of the affected areas.

Clinical course of patients who did not meet the 2005 criteria for kidney transplantation

There were 6 patients with CD4 T cell count below 200 cells/mm^3; 3 did not experience opportunistic infections or HIV disease progression; 3 developed AR, and all had functioning grafts with the most recent eGFR ranging between 28 and 72 mL/min/1.73m^2.

There patient with a detectable HIV RNA viral load at KT (3544 copies/mL) did not experience any allograft rejection although developed renal artery stenosis, CMV viraemia and NODAT as a consequence of high tacrolimus concentrations. The patient was switched to a PI-sparing regimen (Etravirine/Raltegravir/lamivudine) and at last clinic visit eGFR was 64 mL/min/1.73m^2 and HIV RNA < 50copies/mL.

The patient with a history of extra-cutaneous (pulmonary and hepatic) Kaposi sarcoma did not experience recurrent KS. Two of the four patients with hepatitis C were viraemic (HCV RNA > 700,000 IU/mL). One of the patients with with replicating HCV (genotype 1b) acquired HCV infection while awaiting transplantation; he was retrospectively diagnosed with HCV and had cirrhosis on liver biopsy 18 months post-KT. This patient died almost 3 years post-transplant from liver failure; the HCV RNA viral load at the time was 1, 227, 842 copies/mL.

Review at last clinic visit

The median follow-up for the entire cohort was 2.6 (IQR 1.6, 4.6) years. At the last clinic visit, almost half of patients (n=37) were on triple immunosuppressant drug therapy agents; 46% (n=35) were on dual IS therapy and 63% (n=48) included corticosteroids. The overall median eGFR was 46 (35, 63) ml/min per 1.73 m^2 of body surface area (CKD Stage 3). Blood pressure control was slightly suboptimal with median systolic 138 (125, 147) and diastolic 84 (76, 90) mmHg (Reference systolic 130 and diastolic 80 mmHg (Baker et al., 2011)). Majority of patients 89% (n=69) were on a median of 2 anti-hypertensives. Antihypertensives included: calcium channel blockers (n=30); angiotensin converting enzyme inhibitors (n=18); angiotensin II receptor antagonist (n=20); betablockers (n=24); alphablockers (n=25); and diuretics (n=8). When stratified by CNI choice at last clinic visit, blood pressure control was good and similar between groups with patients on ciclosporin vs. tacrolimus achieving a median systolic blood pressure of 138 (123, 144) vs. 137 (127, 150) mmHg (p=0.85) and diastolic blood pressure of 80 (74, 85) vs. 85 (75,90) mmHg (p=0.17) respectively.

New onset of diabetes after transplantation (NODAT) was reported in 4 patients all of whom were taking Tac based IS therapy and PI-sparing cART. Two female recipients had three successful pregnancies through natural conception; all new-borns were HIV DNA PCR negative at birth.

One patient, 62 years of age developed a non ST-segment elevation myocardial infarction (NSTEMI) during plasma exchange therapy for antibody mediated rejection. This patient had a history of endocarditis at 12 years of age. The patient underwent percutaneous coronary intervention (PCI) however required a second PCI after 6 months for in-stent restenosis (ISR) despite dual antiplatelet therapy (aspirin plus clopidogrel).

3.4. Discussion

This is the first study in the United Kingdom to substantiate the feasibility of kidney transplantation in HIV infected individuals with fully suppressed HIV RNA levels maintained on cART. Outcomes from this national observation cohort study reports favorable patient and graft survival, low incidence of post-transplant complications albeit; with a high incidence of delayed graft function (21%) and acute allograft rejection with almost one third of first AR episodes occurring within the first 3 months post-KT. Findings from this carefully selected HIV+ cohort provide further support for the use of KT in HIV positive patients.

Patient and Graft Survival

In the UK general population (UKT), patient survival post-kidney transplantation at 1, 2, and 5 years is 95-99%, 93-98% and 86-95% respectively. Graft survival at 1, 2, and 5 years respectively is 91-97%, 90-95% and 85-92% (NHSBT, 2015). These rates were similar to the UK HIV/KT cohort (at 1, 2, 5 years respectively, patient survival 97.4%, 97.4% and 90.1% vs graft survival 97.4%, 97.4% and 82.3%). This accepts the first hypotheses *(H_0 1.1 and H_0 1.2)* that those kidney transplantation outcomes in HIV infection were comparable in terms of patient and graft survival compared to the general UK population. At baseline, the current cohort was typically young (median age 45 years), male (67%) and with one third having received an allograft from a living donor. Similarly, in the general UK KT population recipients are young (~30% aged 35-49 years), male (~60%) with 34% of allografts from living donors (NHSBT, 2015). There was a higher proportion of patients of black ethnicity in the UK HIV/KT cohort in comparison to the general population, 74% vs. 8% (NHSBT,

2015). This difference in ethnic proportions has been reflected in the transplant waiting times where HIV+ patients had longer waiting times (median 5 years) compared to the general population (median 2.7 years (NHSBT, 2015)). An analysis of KT recipients of black ethnicity alone, the median transplant waiting time for HIV+ patients was 6 years compared to 3.4 years in UKT population (NHSBT, 2015). Although, this is representative of the low ethnic minority donor pool (NHSBT, 2015). What was encouraging was the increasing uptake of kidney transplantation in the HIV infected population over the study period (see **Figure 15**). Although not ascertained in the present cohort, the long waiting times on permanent renal replacement therapy in the HIV+ population may have impacted the patient and graft survival as is suggested in the literature for HIV negative KT recipients (Meier-Kriesche et al., 2000, Meier-Kriesche and Kaplan, 2002). In a HIV negative KT study, the 5 year allograft survival of pre-emptive transplantation observed was 85% compared to 75% in those who were on dialysis 3 to 4 years prior to transplantation (Meier-Kriesche et al., 2000).

The United States of America have reported similar outcomes in HIV/KT recipients. Patient and graft survival rates respectively were 94.6%, 90.4% at 1 year and 88.2%, 73.7% at 3 years (n=150) (Stock et al., 2010a). The careful selection of HIV+ individuals for transplantation has been implicated in the favorable outcomes observed (Stock et al., 2001, Roland and Stock, 2003, Stock et al., 2003b, Stock and Roland, 2007, Stock et al., 2010a). Chapter 1 of this thesis discusses the early experience of kidney transplantation both in the pre-HAART and early HAART era. A review of the literature during this period (pre-2005) highlighted the association of HIV disease factors (i.e. CD4+ T cell

counts, HIV RNA levels and history AIDS defining illnesses) with adverse post-KT outcomes (Roland and Stock, 2003). There was consensus from the early pilot studies(Stock et al., 2003a), US NIH study (Stock et al., 2010a) and UK guidelines (Bhagani et al., 2006) that HIV/ESKD selection criteria to include CD4+ T cell counts >200 cells/mm^3, undetectable HIV RNA levels (<50copies/mL) and no prior history of opportunistic infections. Although, improvement with opportunistic infection prophylaxis and anecdotal evidence of ineligible HIV+ patients with histories of many opportunistic diseases having no recurrences post-KT (Roland, 2004); expanded the selection criteria. One report described 2 patients that were ineligible because of history of pneumocystis jiroveci pneumonia and CMV disease in one case and history of Kaposi's sarcoma and CMV disease in another patient both with no recurrence of OI diseases (Roland, 2004). In the UK, emphasis was placed on AIDS defining illnesses following successful immune reconstitution with cART and history of neoplasms/infections that were considered high risk of re-activating with immunosuppression (Bhagani et al., 2006). In the current report, patients (n=6) were considered ineligible because of: CD4+ cell counts < 200cells/mm^3, although with undetectable HIV RNA levels; detectable HIV (VL >3544 copies/mL); and history of extra-cutaneous (pulmonary and hepatic) Kaposi sarcoma, had positive post-KT outcomes and maintained undetectable HIV RNA levels. However, severe/progressive hepatitis C co-infection resulted in a fatality in one patient. HCV infection, although not a contraindication in the HIV negative population, is associated with increased morbidity and mortality post-KT (Baid-Agrawal et al., 2014). Outcomes from the US NIH study (Stock et al., 2010a) were significantly worse for HCV/HIV co-infected KT recipients with patient/graft survival rates of 88.3%/88.6% at 1 year respectively compared to

HCV negative HIV/KT recipients, 96.1%/90.1% at 1 year. Furthermore, HCV/HIV co-infection was associated with significantly higher rates of serious infections (KM estimates per follow-up year 0.8 vs. 0.5, logrank P = 0.02). However, the emergence of newer anti-HCV therapies, direct acting antivirals (DAAs), that could potentially cure and completely eradicate HCV may possibly improve outcomes for HCV/HIV KT recipients.

Allograft outcomes

Allograft outcomes were complicated by the high rejection rates, almost double those noted in UK general population, 36% vs 12-24% at 1 year respectively (Summers et al., 2010, Summers et al., 2013). This rejects the third hypothesis (*H_0 1.3) that kidney transplantation in HIV-positive patients has associated allograft rejection rates comparable to the general UK population.* When compared to the USA study of HIV/KT, our time to first AR rates at 1 year were similar, 36 vs 31% respectively (Stock et al., 2010a). The reason for this high incidence of rejection has not been fully elucidated however, what has been postulated is a combination of HIV associated immune reactivation and sub-optimal immunosuppression (Trullas et al., 2005, Roland et al., 2008b, Stock et al., 2010b, Canaud et al., 2014). Analyses of the factors associated with AR in this cohort are presented and discussed extensively in Chapter 4.

In the present analysis, there was no donor/recipient factor found to be associated with DGF development (data not shown). Mazuecos et al (2013) in an observational study that included HIV negative controls, observed a high incidence of DGF in the HIV+ population (52% vs. 21%, P < 0.001). The rate of DGF in the HIV/KT population has been variable; Stock et al (2010) observed a

rate of 46% (n=150), Roland et al (2008) 50% (n=18), Touzot et al (2010) 28% (n=27), Panarey (2015) 46% (n=39), Kershaw et al (2015) 52% (n=33), Kucirka et al (2015) 30-40% (n=315). A high rate of DGF among HIV/KT recipients could be multifactorial to include donor characteristics, quality of the allograft and recipient characteristics. Although multiple risk factors for developing DGF have not been accounted for in this present analysis such as cold ischaemic time (CIT), anastomosis time, donor age and deceased donor allograft type i.e. after cardiac or brain death, donor body mass index (Irish et al., 2010, Doshi et al., 2011, Weissenbacher et al., 2012, Marzouk et al., 2013, Mazuecos et al., 2013), there are other plausible HIV independent risk contributing factors. Mazuecos et al (2013) multivariable analyses identified HIV infection, HCV co-infection and CIT as predisposing factors to developing DGF in HIV/KT recipients. Prolonged duration of pre-transplant dialysis has also been suggested to predispose HIV/KT recipients to DGF (Schweitzer et al., 1998, Panel de expertos del Grupo de Estudio de Sida y del Plan Nacional sobre el, 2010, Doshi et al., 2011, Weissenbacher et al., 2012). Vascular calcification frequently observed in patients on prolonged dialysis is thought to delay the anastomosis time thereby increasing the risk of developing DGF post-KT. Furthermore, persistent residual kidney function in patients on short term dialysis may promote early graft function (Schweitzer et al., 1998, Vercauteren et al., 2003). Prolonged pre-transplant dialysis time is common among HIV/ESKD especially in those with co-infection (e.g. HCV) (Moutinho et al., 2005, Fabrizi, 2013, Mazuecos et al., 2013). In the UK general population, differences in DGF rates by deceased donor type i.e. heart beating or non-heart beating donor has been observed; 24% compared to 48% in the latter group. Similarly, there was a low incidence of primary non-graft function (PGNF)

observed in the UK HIV/KT cohort. PGNF in the HIV negative kidney transplant population have been observed similar rates, 4.9 – 5.7% HIV- vs 5% in current HIV+ cohort (Weber et al., 2002b, BTS, 2005).

Although the post-transplant course of allograft function was significantly worsened by experiencing allograft rejection. These findings were not dissimilar to the USA HIV/KT NIH study that reported eGFR at 1 year of (51.8 AR vs. 60.5 no AR ml per minute per 1.73 m^2, P=0.05) although, the AR group seemed to have significantly worse outcomes (Stock et al., 2010a). Outcomes were also comparable to the general population. In the PORT (Patient Outcomes in Renal Transplantation) study, a multinational global study (n=13,671), majority of patients (55 to 60%) had stage 3 CKD after 1 year post-transplant (Kasiske et al., 2011). Graft function was worsened by allograft rejection at 1 year. The rate of AR was 23% (n=3145), of whom 53% had an eGFR <44 ml per minute per 1.73 m^2 at 1 year. In a recent UK national kidney transplant trial (n=852) reported graft function at 6 months post-transplant of eGFR 49.8 – 50.1 ml per minute per 1.73 m^2 (3C.StudyCollaborativeGroup et al., 2014).

Post-transplant complications

Opportunistic infections

Opportunistic infections (OI) overall were uncommon in the present HIV/KT dataset (41%). CMV infection was the most common OI occurring in a quarter of the HIV/KT recipients. In solid organ transplantation, CMV infection can occur as a primary or latent viral infection. CMV disease is associated with increased morbidity and mortality owing to the detrimental effects to the allograft and other native organ (Rubin, 1989). CMV disease can occur in the retina, lung,

gastrointestinal tract, central nervous system, liver, biliary tract, heart and adrenal glands (Torres-Madriz and Boucher, 2008, Nelson et al., 2011). It is the most commonly occurring OI in the general solid organ transplant population with 8 - 39% overall and 8% among kidney transplant recipients expected to experience symptomatic CMV infection (Patel et al., 1996, BTS, 2011). The prevalence of kidney transplant recipients considered at risk of developing CMV disease has been estimated to be 30% in the UK (Newstead, 1995). Although, this rate is influenced by the matching of the donor/recipient CMV IgG serology and the multiple strains of CMV (Grundy et al., 1988) (BTS, 2011). CMV seroprevalence among the general adult population is approximately 70 to 90% (Kasiske et al., 2010, Kuo et al., 2010, Requiao-Moura et al., 2015). The distribution of donor/recipient CMV IgG serology matching in the general KT population has been reported as follows: D+/R+, 47.7%, D-/R+, 24.1%, D+/R-, 18.2%, and D-/R-, 10.3% (Kuo et al., 2010, Requiao-Moura et al., 2015). CMV infection among HIV positive individuals in the pre-HAART era was one of the leading causes of HIV disease progression often associated with immunodeficiency (Nelson et al., 2011). Antiretroviral drugs have significantly improved the occurrence of CMV disease to an estimated 4% (Kim et al., 2006) from 20 – 40% previously (Nelson et al., 2011). However, there is a high CMV seroprevalence among HIV positive patients which is in excess of 90% (Kim et al., 2006, Asboe et al., 2012). Furthermore, detectable CMV viraemia has been reported in 20 to 60% of HIV positive patients on HAART and with CD4 T-cell counts < 100 cells/mm^3 (Bowen et al., 1997, Spector et al., 1998, Wohl et al., 2009). The use of primary chemoprophylaxis by HIV positive individuals has not been proven to be effective in the prevention of CMV disease. Consequently, CMV DNA is therefore not routinely monitored and use of primary CMV

prophylaxis is restricted to HIV+ individuals with a CD4 T count < 50 cells/μL, persistent CMV viraemia and no HIV treatment options. Secondary prophylaxis is also not routinely recommended except for relapse of CMV pneumonia or CMV oesophagitis with concomitant ophthalmological disease (Asboe et al., 2012).

In the general KT population, the use of primary prophylaxis is much debated. There are two approaches that are utilized in the prevention of CMV disease in KT recipients. Briefly, universal prophylaxis involves the administration of low dose antivirals for a prolonged period post-transplantation. Administration of low dose valganciclovir for 100 days reduced rate of CMV disease to 5% in all patients and to 15% among those at risk of primary CMV infection (Gane et al., 1997, Singh, 2001). This approach, however, has cost implications, increased risk of drug resistance, and drug toxicity. Preemptive therapy involves initiating prophylaxis in select high-risk transplant recipients (D+/R-) with asymptomatic CMV viraemia (Gane et al., 1997, Fischer et al., 2013). CMV infection is low among D+/R+ and D-/R+ among solid organ transplant recipients (BTS, 2011) which supports the use of preemptive therapy. However, this approach is limited by the cost and practicalities of CMV surveillance and the reliability of the diagnostic tests (Winston, 1995, Fischer and Masur, 1997, Singh, 2001). Furthermore, antivirals used during periods of high viral burden can be ineffective and promote emergence of CMV resistance (Drew et al., 1991, Rosen et al., 1997, Singh, 2001). This has also been observed in the HIV positive non-transplant patients where preemptive anti-CMV therapy proved ineffective in preventing CMV end-organ disease (Wohl et al., 2009). In the United States, KDIGO guidelines recommend universal CMV chemoprophylaxis for at least 3 months except where both donor and recipient have negative

serology (Kasiske et al., 2010). A recent national study (n=315) reported an overall < 10% proportion of HIV kidney transplant recipients that developed infections in the first year post-transplant (Kucirka, 2015). Although it has been argued that the use of antithymocyte globulin induction therapy increases the risk of CMV infection in HIV/KT recipients, Kurcika et al (2015) found ATG to have a lower risk compared to other groups (3.8% ATG, 8.7% anti-CD25 and 7.9% with no induction). In the present study, more than a quarter of patients developed CMV infection 5 of whom had received chemoprophylaxis. These results may suggest that universal prophylaxis may be protective in HIV/KT recipients although, further study in a larger cohort is warranted.

Other viral infections such as BK virus and Epstein-Barr virus can also adversely affect kidney transplant outcomes. In the present study there was a low occurrence of BKV and EBV infections with 3 cases of BKV neprophathy (BKVN) and 1 case of PTLD. Results from a sub-study of the US NIH HIV/KT multisite trial, BKV viraemia occurred in 25% (n=137), biopsy proven BK associated nephropathy in 9 (7%) patients (Hirsch, 2013) and there were no cases of PTLD (Stock et al., 2010a). In the multivariable analyses, acute rejection was the only factor that was marginally associated with risk of developing BK viraemia (AR (HR: 2.0; 95% CI: 0.9-4.0; p=0.07)). Outcomes for both US NIH and present study were similar to the HIV negative KT population. The BKV seroprevalence in the general adult population is estimated at 60 to 80%. BKV reactivation from the allograft is suggested to be the cause of viraemia and viruria in the general KT population. BKVN might further develop in 1 to 10% of the general KT population which may result in graft loss in 10 to 80% (Comoli and Ginevri, 2012, Comoli et al., 2013, Mutlu et al., 2015). PTLD in the general KT population is uncommon (1 to 3%) but if acquired is

associated with a high risk of mortality. Approximately 90% of the adult population by age 40 is reported to have developed antibodies to EBV. There are no antiviral drug therapies available to treat or prevent BKV or EBV; management includes reduction in immunosuppression (Cockfield et al., 1993, Weikert and Blumberg, 2008).

Malignancy

Tumors and neoplasia were infrequent in the present study (8%, n=6). Findings were similar to the US NIH trial that reported 14 (8.7%) malignancies (skin cancer (n=5), cutaneous Kaposi's sarcoma (n=3), penile squamous cell cancer (n=1), head and neck cancer (n=3) and renal cell cancer (n=2)) over a 3.5 year follow-up period (Nissen et al., 2012). Both in the current and US studies, the KS cases responded to treatment with sirolimus. These results are not dissimilar to the HIV negative kidney recipients. The incidence of malignancy in the HIV negative KT population is reported to be 3 to 5 times higher than the general population (Birkeland et al., 2000, Zeier et al., 2002, Morath et al., 2004). Immunodeficiency is thought to be the causal factor that increases the risk of cancer in both the transplant and HIV/AIDS populations (Grulich et al., 2007).

An epidemiological study that compared HIV negative kidney transplant recipients to the general population observed a 13.8 fold increased risk of cancer in the former group (Yang et al., 1998). In the non-transplant HIV population, there is a substantially increased risk of cancer compared to the general population particularly for the AIDS defining cancers. In a meta-analysis that examined the incidence of cancer in the HIV/AIDS (7 studies, n=444 172) and transplant (5 studies, n=31 977) populations reported significantly higher

incidences of cancer compared to the general population. For three main types of AIDS defining cancers, all HPV related cancers and Hodgkin's lymphoma the SIR (95 CI) was HIV/AIDS 11·03 (8·43–14·4); transplant 3·89 (2·42–6·26. In this study, HIV infected individuals were 70 times, 25 times and 5 times more likely to be diagnosed with Hodgkins lymphoma, anal and cervical cancers respectively than the general population (Grulich et al., 2007). In a recent registry study over a 14 year period (1996 – 2010), the proportion of cancers reported were similar for HIV positive individuals and transplant recipients 0.02% (n=4.7million) and 0.01% (9.7million) respectively (Shiels MS, 2014). However, no association has been found on whether solid organ transplantation further increases the risk of developing cancer in the HIV infected population (Nissen et al., 2012). Although, the authors observed an increased risk of progression of human papilloma virus (HPV)-associated neoplasia to high grade squamous intraepithelial lesions in 89 HIV/KT recipients whom were followed for anal cytology. This highlights the importance of anal and cervical surveillance in the HIV/KT population. In the present study, data were sparse on anal and cervical cytology therefore not reported.

HIV virological control and disease progression

In the current cohort, there was no evidence of accelerated HIV disease progression. Likewise, in the USA NIH study there was no evidence of advanced HIV disease. However, there were two cases of HIV associated nephropathy that recurred post-transplant in the USA cohort despite having undetectable HIV viral load (<50cps/ml) (Stock et al., 2010b). Although, FSGS may have been the differential diagnosis as it is the predominant (~30%) kidney

disease that reccurs post-KT in the general population (Ponticelli and Glassock, 2010).

In both cohorts, there were two cases each of Kaposi Sarcoma; and only one case of PTLD in the UK cohort. In the general KT population, the prevalence of Kaposi Sarcoma varies between geographical regions. The prevalence of Kaposi Sarcoma in Europe is estimated at 1.6%; Australia and USA by comparison is 24% and 1.6% respectively (Tan and Goh, 2006, Raeisi et al., 2013). Kaposi Sarcoma in general KT population approximately 82% of all cases occur within 2 years of receiving an allograft (Bouwes Bavinck et al., 1996, Mbulaiteye and Engels, 2006). Kaposi Sarcoma is associated with HHV-8 reactivation that may be induced by immunosuppressive treatment.

There was no loss in HIV virological control with the use of immunosuppressive therapies or with the associated decline in CD4 T cell counts. However, there were cases of transient low level HIV viraemia in both cohorts. HIV viral load blips are common in the general HIV population on cART (Asboe et al., 2012, Young et al., 2015). HIV VL blips have been suggested to be due to reduced antiretroviral drug concentrations (Kieffer et al., 2004, Persaud et al., 2004, Nettles et al., 2005, Dinoso et al., 2009, Asboe et al., 2012).This was not ascertained in both the current dataset or the USA NIH study. However, concerns of HIV viral rebound are considered when HIV VL > 500 copies/mL (Martinez et al., 2005, Grennan et al., 2012, Young et al., 2015). It is therefore not a reason to alter antiretroviral drug therapy (Asboe et al., 2012). It has been suggested the variation in HIV RNA testing and non-adherence could be contributory factors (Asboe et al., 2012, Garrett et al., 2012). Another theory is the possible HIV reservoir replenishment brought about antigen stimulation of latently infected cells (Jones and Perelson, 2007). This could explain the

observation made by Canaud et al (2014) where they found HIV-1 had infected the kidney allograft after transplantation despite undetectable HIV viraemia.

In the pre-HAART era, there were concerns that use of immunosuppressive agents may enhance HIV disease progression. However, through various mechanisms immunosuppressant drugs have demonstrated anti-HIV properties (Roland, 2004). While there were cases in the present cohort of Kaposi Sarcoma, an AIDS defining illness, the rate was not dissimilar to the general KT population (Shiels MS, 2014). All Kaposi Sarcoma patients were successfully treated with sirolimus. In early HIV/KT studies, there were concerns of acceleration of AIDS defining illnesses particularly with the use of immune depleting agents (Stock et al., 2001). This has not been observed in both the USA NIH study and the current dataset (Stock et al., 2010a).

Other post-transplant complications were few. New onset of diabetes after transplantation occurred in only 4 (5%) patients on tacrolimus based therapy. The prevalence of NODAT in general KT population varies between 2 to 53% (Balla and Chobanian, 2009, Sarno et al., 2012, Palepu and Prasad, 2015). Between the calcineurin inhibitor agents, tacrolimus is 50% more likely to induce diabetes than ciclosporin (Kasiske et al., 2003, Woodward et al., 2003, Palepu and Prasad, 2015).

There was no increased risk of developing cardiovascular disease (CVD) although; a longer follow-up is necessary to draw this inference. The one case of non-ST segment elevation myocardial infarction was precipitated by plasma exchange. This patient had no prior history of cardiovascular disease. CVD is associated with increased morbidity and mortality among kidney transplant recipients. The annual rate (fatal/non-fatal) of CVD events in the general KT

population is 3.5 to 5.0% which is 50 fold greater than the wider general population (Fishbane, 2005, Kidney Disease: Improving Global Outcomes Transplant Work, 2009). Other additional factors such as obesity, diabetes, hypertension, and proteinuria can further contribute to CVD risk in the KT population (Metcalf et al., 1992, Fernandez-Fresnedo et al., 2002, Fishbane, 2005, Jeon et al., 2015). Furthermore, HIV infection is an independent risk factor for developing CVD (Triant, 2012). Some antiretroviral medication use (e.g. abacavir) has also been associated with increased risk of CVD (D.A.D.StudyGroup et al., 2008, Friis-Moller et al., 2015). Preventative measures and close monitoring is therefore warranted in the HIV/KT cohort in order to mitigate CVD. Post-transplant blood pressure control is one example. In the current cohort, at the last clinic visit blood pressure control was good with median systolic 138 (125, 147) and diastolic 84 (76, 90) mmHg with almost 90% of patients being maintained on 2 blood pressure control medication. The KDIGO guidelines suggest that post-KT blood pressure should be maintained at <130/80mmHg (Kidney Disease: Improving Global Outcomes Transplant Work, 2009).

The strength of the current study is its size and duration of follow-up. This study is the largest HIV/KT cohort in Europe (Trullas et al., 2010) and comparable to the USA NIH Study. With the exception of three patients, the remaining patients had a minimum of one year of follow-up and the median follow-up was nearing 3 years. Nonetheless, the study had some limitations. First, as the observational cohort study design where multiple data sources were used may have introduced information bias but also prevented standardization (Vandenbroucke et al., 2014). The evolution of HIV and renal care over the long study period also contributed to non-standardised management. For example, an

independent blinded biopsy review including protocol biopsies may have strengthened allograft rejection findings. Information was lacking that may have introduced confounding e.g. sensitization (from blood transfusions, pre-transplant pregnancies, etc), calculated reaction frequency, cold ischaemic times, proteinuria and donor specific antibodies. The high proportion of patients of black ethnicity may have also been a confounding factor. Cytochrome P450 3A5 expressers, that have significantly higher dose requirements of certain immunosuppressant drugs (e.g. tacrolimus), are more prevalent in black ethnic KT recipients compared to other ethnicities (Macphee et al., 2002, MacPhee et al., 2004, Macphee et al., 2005, Moreton et al., 2005, Vadivel et al., 2007, Spierings et al., 2013). Variation in human leukocyte antigen polymorphisms and having a stronger immune response are some of the explanations offered for the disparity of immunological responses between ethnic groups (Milford et al., 1987, Opelz et al., 1989, Gordon et al., 2010).

3.5. Conclusion

The analysis confirms the feasibility of kidney transplantation in carefully selected HIV infected individuals. Favourable outcomes may have been attributable to the stringent selection criteria including fully suppressed HIV, being maintained on cART and with a somewhat recovered immune status. The safety of post-transplant immunosuppression was demonstrated by lacking evidence of HIV disease progression, AIDS defining illnesses or tumours/neoplasms. Allograft rejection complicated post-transplant outcomes. The complex immunosuppressant and antiretroviral drug interactions are suggested to have contributed to suboptimal immunosuppression. This hypothesis has been explored in Chapter 5. Strategies that could be explored to improve post-allograft outcomes include the use of more potent induction immununosuppressive therapies and integrase inhibitor based antiretroviral drug regimens to avoid drug interactions. Although not explored in the present analysis, having defined donor selection criteria may also contribute to having optimal allograft outcomes. Finally, the current cohort requires longer follow-up to determine the long-term host/graft survival.

Chapter 4. Calcineurin Inhibitors and Rejection in HIV/KT

4.1. Introduction

The success of kidney transplantation is attributable to the immunosuppressive therapies that target various pathways involved in the native and adaptive alloimmune responses to the allograft (Wolfe et al., 1999, Halloran, 2004, Kaplan and Meier-Kriesche, 2004, Sayegh and Carpenter, 2004). Over the past 50 years, the use of immunosuppressive agents have vastly improved patient and graft survival rates post-kidney transplantation (Sayegh and Carpenter, 2004). However, there were long term risks of developing adverse events with life-long immunosuppression (Kaplan and Meier-Kriesche, 2004). Subsequently, there has been progressive development in the optimisation of immunosuppressive therapy by combining the different agents and personalising therapies to meet individual patient's needs (Sayegh and Carpenter, 2004, Azzi et al., 2013). However, achieving immune tolerance still remains the ultimate dream of clinicians (Ruiz et al., 2013).

There are three main pathways that achieve immunosuppression including: (i) lymphocyte depletion, (ii) blockade of lymphocyte responses, or (iii) diverting lymphocyte traffic (Halloran, 2004) as shown in Figure 21.

Figure 21: Diagram of T-cell Mediated Rejection and the different mechanisms of action of immunosuppressive drugs

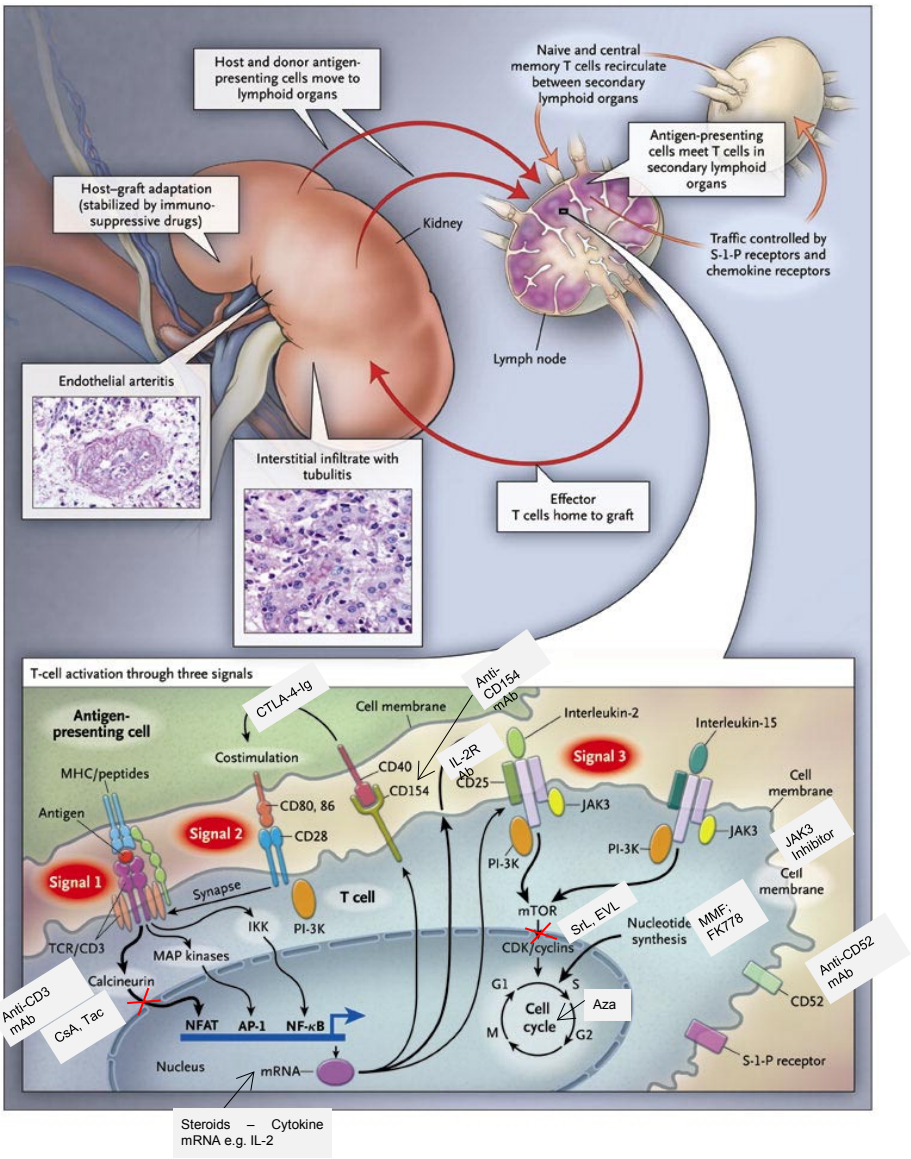


Figure adapted from "Immunosuppressive Drugs for Kidney Transplantation."by Philip F. Halloran, M.D., Ph.D. 2004, New England Journal of Medicine; 351:2715-2729.

When kidney allograft is inserted into the recipient, there are three distinct signalling pathways that are activated in the process of rejecting the transplanted organ. **Signal 1** occurs when the antigen presenting cells (APCs) initially migrate to T cell areas of secondary lymphoid organs to present the donor antigens to the naïve and central memory T cells (TCEM). When the APCs present the donor cells and activate the T cells through the T-cell receptor (TCR), the naïve T cells start to modulate expression of surface molecules that are associated with activation, costimulation and adhesion (Expansion of activated human naïve T-cells precedes effector function (Brenchley et al., 2002). **Signal 2** then occurs when CD80 receptor expressed on the APC engages the CD28 receptor expressed on the surface of the T cell. The resulting costimulation response activates 3 signal transduction pathways (a) calcineurin pathway (b) mitogen activated protein (MAP) kinase C-nuclear factor-KB (NF-KB) pathway which activates transcription factors – nuclear factor of activated T cells (NFAT), NF-KB and activating protein-1 (AP-1). This up-regulates expression of CD154, CD25 and releasing interleukin-2 (IL-2) cytokine. Subsequently, several cytokines are released that deliver growth signals thus initiating the cell cycle (**Signal 3**). This includes the molecular target of rapamycin (mTOR) pathway. Further, to complete the cell cycle and for lymphocyte replication to occur, synthesis of purine and pyrimidine nucleotides are required. Both proteins are regulated by inosine monophosphate dehydrogenase (IMPDH) and dihydroorotate dehydrogenase (DHODH), respectively. The T cells exposed to the donor antigen then migrate to and penetrate the allograft to destroy it. This process leads to the development of lesions such as tubulitis and endothelial arteritis. To deter this rejection process, immunosuppressive drugs target the different signalling pathways as depicted in the figure.

Key: CsA, Ciclosporin; Tac, Tacrolimus; Aza, Azathioprine; MMF, Mycophenolate; SrL, Sirolimus; EVL, Everolimus; IL-2R Ab, Interleukin-2 receptor α chain (anti-CD25, basiliximab); anti-CD52, Campth-1H; JAK3, Janus kinase 3; IKK, denotes inhibitor of nuclear factor-KB kinase; PI-3K, Phosphoinositide-3-kinase pathway; S-1-P, Sphingosine-1-phosphate receptors; MHC, Major histocompatibility complex; CTLA-4-Ig, Cytotoxic T lymphocyte-associated molecule-4 (belatacept).

Lymphocyte depletion includes immunosuppressive agents that aim to destroy T cells, B cells or both. Examples of such agents include: polyclonal antibodies derived from horse or rabbit, anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG) respectively; mouse monoclonal anti-CD3 antibody (withdrawn from market); humanised monoclonal anti-CD52 antibody (alemtuzumab); and B-cell depleting monoclonal anti-CD20 antibody (rituximab) (Halloran, 2004). Non-depleting antibodies include: monoclonal anti-CD25 (Salis et al., 2008); and T cell costimulation (CD28/CD80) blockade agent (belatacept) (Vincenti et al., 2016). There are other antibody targets that have been trialled or under development for example, anti-CD154 which was withdrawn due to thromboembolic complications (Koyama et al., 2004); and anti-CD2 – multiple agents have been trialled but failed to demonstrate superior allograft outcomes (Squifflet et al., 1997, Rostaing et al., 2013).

In the early 1960s, the development of mercaptopurine-6 and azathioprine led to the use of immunosuppression as standard of care post-transplantation (Elion, 1993). Although, early experience with the nonselective cytotoxic agents was associated with undesired toxicity attributed to the suppression of other rapidly proliferating cells in the bone marrow and gastrointestinal tract (Hardman et al., 1996a). The discovery of more selective immunosuppressive agents (e.g. calcineurin inhibitors) revolutionised the management of allograft recipients, as they dramatically improved both host and graft outcomes (Azzi et al., 2013). Calcineurin inhibitors are the mainstay IS agents that have been in use since the 1980s (Azzi et al., 2013). Other agents that target different lymphocyte reponses include: T- and B-cell antiproliferative mycophenolate (Remuzzi et al., 2004); mechanistic target of rapamycin (mTOR) inhibitors

sirolimus (Morath et al., 2007) and everolimus (Pascual, 2009); and Janus kinase (JAK) 3 inhibitor tofacitinib (Wojciechowski and Vincenti, 2011).

Discovery & Pharmacology of Calcineurin Inhibitors

Calcineurin, a calcium dependent protein phosphatase, is triggered during T-cell antigen receptor (TCR) mediated activation which in turn dephosphorylates nuclear transcription factors (NF-AT, nuclear factor of activated T-cells) that mediate cell survival and expression of cytokines. This process produces proinflammatory responses that results in allograft rejection. By binding to specific endogenous cytosolic proteins, immunophilins, results in calcineurin inhibition. Calcineurin inhibitors interfere with these alloimmune reponses to prevent rejection (Peakman and Vergani, 2009, Sanchez-Fueyo and Strom, 2011). Both ciclosporin and tacrolimus have similar pharmacodynamics properties by inhibiting calcineurin (Azzi et al., 2013).

Ciclosporin

Ciclosporin was the first calcineurin inhibitor discovered in the early 1980s by Dr. Sandor Lazary and Dr. Jean-Francois Borel at the Sandoz Company in Basel, Switzerland. Ciclosporin is a cyclic polypeptide isolated from a fungus *Tolypocladium inflatum Gams* which binds to cyclophilin and the resulting complex inhibits calcineurin (Hardman et al., 1996b, Rang and Dale, 2012).

Tacrolimus

Tacrolimus like ciclosporin is derived from fungus in particular *Streptomyces tsukubaensis*. It inhibits calcineurin by binding to FKBP-12 protein, an

immunophilin that plays an important role in the T-cell activation process (Hardman et al., 1996b, Rang and Dale, 2012). Unlike cyclophilin which is widely abundant in the body (Wang and Heitman, 2005), FKBP proteins are present in FKBP-expressing cells found in the cellular component of whole blood. Lymphocytes in particular, highly express FKBP proteins (Baughman et al., 1997, Yura et al., 1999, Galat, 2003).

Early Calcineurin Inhibitor Clinical Studies in HIV negative KT recipients

Although calcineurin inhibitors are potent immunosuppressive agents, the complexities of the immune activation responses following kidney transplantation require for the combined use of multiple immunosuppressant drugs for the prevention of allograft rejection. The first human clinical trial used ciclosporin monotherapy for deceased donor kidney transplantation in seven patients on dialysis. Initial results showed no signs of rejection however; six patients required the addition of a cyclophosphamide analogue to manage interstitial inflammation associated with mononuclear infiltration, one experienced graft loss due to pyelonephritis and one died with disseminated aspergillosis (Calne et al., 1978). A follow-up study by Calne et al (1979) using ciclosporin monotherapy in 34 transplant patients (32 kidney, 2 pancreas, 1 liver) showed promising results with 82% overall patient 1-year survival and 81% kidney graft survival at 1 year; 19% (n=6) rejection rate. Although, in 20 patients the addition of a cyclophosphamide analogue was required and a further six additional steroids to optimise the immunosuppressive therapy. The intensification of the immunosuppression resulted in severe infectious and malignant complications (Calne et al., 1979). Very soon after, a large

multicentre European trial was conducted in 232 deceased donor kidney transplants randomised into ciclosporin monotherapy (n=117) vs azathioprine (n=115) plus steroids groups. The results at 1 year showed excellent results in favour of ciclosporin compared to the control group respectively, 99% vs 92% patient survival, 72% vs 52% graft survival and 19% vs 9% acute rejection rate. However, in the ciclosporin group 24 out of 84 with remaining functioning grafts at 1-year were switched to azathioprine plus steroids for the treatment of allograft rejection (n=18) and to avoid CNI related adverse events (n=6); 1 had additional steroids and 59 remained on CsA monotherapy. No differences were noted in the rates of infection although, it was noted that those in the ciclosporin arm had worse renal function. It was soon discovered that the poor renal function was due to the nephrotoxic properties of ciclosporin (EuropeanMulticentreTrialGroup, 1983). Interestingly, graft survival was better in the ciclosporin group despite having more frequent rejection episodes and despite using higher doses than we currently use today (17mg/kg/day vs 10mg/kg/day (NovartisPharmaceuticals, 2014), respectively) (EuropeanMulticentreTrialGroup, 1983). Further evidence emerged that suggested the use of ciclosporin monotherapy was effective for preventing allograft rejection however; adverse events such as nephrotoxicity also became evident (Azzi et al., 2013).

A Canadian multicentre, randomised trial that included 209 deceased donor kidney transplant recipients was among the first studies that looked at combining ciclosporin plus steroids to ascertain if it would improve outcomes. Their results were somewhat better than the European trial with 97% vs 86% 1-year patient survival and 80% vs 64% 1-year graft survival in those taking CsA

plus steroid compared to Aza plus steroid. There were 159 treated rejection episodes in the ciclosporin group compared to 157 in the control group. This study also used much higher ciclosporin doses (20mg/kg loading dose) but aimed for similar C_{trough} whole blood concentrations to what we use today (100-400ng/ml) (CanadianMulticentreTrial, 1983). What established CNIs being used as the main agent for immunosuppressant drug therapy in solid organ transplantation, was a collaborative study from 200 European transplant centres that showed 10 – 15% superiority in graft survival in patients taking ciclosporin based therapy (CsA (n=2,965) vs other (n=6,915) respectively, 78% vs 67% at 1 year p<0.0001) (Opelz, 1986). It wasn't until 1997, 20 years after using ciclosporin that tacrolimus was discovered (Tanaka et al., 1997). Due to the difference in mechanism of action, it was hoped that tacrolimus would have fewer adverse effects including nephrotoxicity however, there was no evidence of this (Williams and Haragsim, 2006).

Early studies that compared tacrolimus with ciclosporin reported dramatic reductions in acute rejection (Tac vs CsA respectively, 25.9% vs. 45.7% P<0.001, n=448 (Mayer et al., 1997); 30.7% vs. 46.4% P=0.001, n=412 (Pirsch et al., 1997)) albeit with no differences in patient or graft survival rates (Tac vs CsA respectively, 1-year patient 93.0% vs. 96.5% P=0.140 and graft survival rates 82.5% vs. 86.2%; P=0.380 (Mayer et al., 1997); 1-year patient 95.6% vs. 96.6% P=0.58. and graft survival rates 91.2% vs. 87.9%; P=0.29 (Pirsch et al., 1997)).

Aside from nephrotoxicity, CNIs were associated with other adverse effects such as hypertension, diabetes, neurotoxicity and dyslipidaemia. This led to looking for strategies to optimise immunosuppressive therapy by minimising or avoiding CNIs to evade related toxicity whilst achieving/maintaining efficacy

(Azzi et al., 2013). The addition of mycophenolate, a potent immunosuppressive agent that selectively inhibits T- and B-cell proliferation, to ciclosporin plus steroids (triple therapy) saw kidney rejection rates as low as 17% (pooled efficacy analysis of three clinical trials n=1493) in the first 6 months post-KT (Halloran et al., 1997). However, early trials observed patients suffering from adverse reactions attributed to mycophenolate to include gastrointestinal reactions, leukopenia and increased opportunistic infections (1995, Sollinger, 1995, Browne, 1996, Halloran et al., 1997). Despite using dual and triple immunosuppressant drug combinations, allograft rejection continued to be problematic and was associated with poorer long-term graft function (Pelletier et al., 1998). This led to the development of more intensive immunosuppressive therapy such as the poly/monoclonal antibodies and lymphocyte depleting agents (Nashan, 2005). One study explored ‘quadruple immunotherapy’ in kidney transplant patients (n=499), comparing ciclosporin plus mycophenolate plus steroid to Aza plus mycophenolate plus steroids with the inclusion of mono/polyclonal antibodies (antithymocyte globulin, ATG; antilymphocyte globulin, ALG; muromonab, OKT3) in both groups. The authors reported first biopsy-proven rejection rates at 6 months of 38% in azathioprine group vs 18% in ciclosporin group (Sollinger, 1995).

The choice of immunosuppressive drug regimen was not the only focus of managing kidney transplant recipients, determining the optimal CNI drug exposure associated with CNI efficacy also became paramount (Grevel et al., 1991, Min et al., 1998, Staatz et al., 2001, Borobia et al., 2009). CNI therapeutic drug monitoring initially used total exposure, AUC, to determine efficacy but this was not practical in clinical practice. Subsequent PK studies aimed to determine the optimal single time point that correlated with total exposure. Some evidence

suggested that peak concentrations (C_{max}) had better correlation to total exposure (AUC) than pre-dose (C_{trough}) concentrations and therefore, were better predictors of allograft outcome (e.g. rejection) (Jorgensen et al., 2002, Felipe et al., 2003, Aoyama et al., 2005, Mardigyan et al., 2005a, Mardigyan et al., 2005b, Takeuchi et al., 2008). However, this was also impractical in the clinical setting. $C_{trough/pre\text{-}dose}$ whole blood concentrations soon became the most commonly used for CNI therapeutic drug monitoring (TDM) (Schiff et al., 2007). However, the wide inter- and intra-patient variability due to multiple influential factors (e.g. food interactions, drug interactions, pharmacogenetics, gender, patient adherence, drug formulation or ethnicity) meant that $C_{trough/pre\text{-}dose}$ drug concentrations did not accurately correlate to total drug exposure (Min et al., 2000, Macphee et al., 2002, MacPhee et al., 2004, Macphee et al., 2005, Acott et al., 2006, Connor et al., 2012, Ro et al., 2012, Spierings et al., 2013); refer to Chapter 5 for further details on CNI drug exposure.

Purpose of study

The main purpose of this chapter is to investigate whether calcineurin inhibitor choice (ciclosporin versus tacrolimus) has an impact on allograft outcomes, specifically allograft rejection in the first year post-kidney transplantation of HIV positive patients. Secondary outcomes include identifying factors associated with allograft rejection in the UK HIV/KT cohort by using univariate and multivariate analyses. Finally, a descriptive analysis of the adverse events mainly reactivation of latent viral infections stratified *a priori* by CNI choice.

Hypothesis

The main hypothesis of this chapter is

H_0: *There will be no differences in allograft rejection rates in HIV positive kidney transplant recipients taking either ciclosporin or tacrolimus based immunosuppression therapy.*

4.2. Method

Study Design

This was a national observational cohort study including 40 Transplant and referring HIV centres. The full details of the study methods have been described previously in Chapter 3 page 109 - 113.

Ethics Approval

This was a multicentre research ethics committee (MREC) approved study. The full details of the ethics and local R&D approvals have been previously described (see Chapter 3 page 109).

Patient Enrolment

Case ascertainment was established by clinicians at the local centres. Data were used from HIV positive individuals over 18 years of age that had a kidney transplant up to 31st December 2013. Enrolled patients were stratified *a priori* by CNI choice at the point of transplantation, ciclosporin (CsA) or tacrolimus (Tac).

Inclusion criteria

1) Patients that acquired HIV prior to kidney transplantation
2) Patients ≥ 18 years of age
3) Patients that took calcineurin inhibitors (CsA or Tac) as part of immunosuppressant drug therapy management in the first year post-transplant

Exclusion criteria

1) Patients that acquired HIV post-kidney transplantation
2) Patients under 18 years of age.
3) Patients that took other non-calcineurin inhibitor based therapy at transplantation for example, mammalian target of rapamycin (mTOR) inhibitors (e.g sirolimus).
4) Patients that had primary graft non-function within 6 months of being transplanted
5) Patients with insufficient/missing/no data

Data Collection

The full study design, case ascertainment and data collection have been previously described in Chapter 3 page 109 - 113. For the purposes of this chapter, the data used included baseline recipient/donor characteristics, HIV management with antiretroviral therapy, immunosuppressant drug therapy management during first year post-KT, patient/graft outcomes and CNI related adverse events as outlined below.

Recipient and Allograft Characteristics

Baseline recipient characteristics include: demographics - age, gender and ethnicity; renal disease background and history of management – renal disease aetiology and date of permanent replacement therapy initiation if applicable; HIV disease background and management – date of HIV diagnosis, HIV risk, antiretroviral therapy at KT; CD4 nadir prior to KT and CD4 count at KT; co-morbidities – hepatitis B or C co-infection, hypertension or diabetes; and for those co-infected, hepatitis B or C viral load.

Allograft characteristics include donor type, HLA mismatch status and donor/recipient CMV mismatch status.

Host/Graft Outcomes

Recipient survival was defined as the time from transplantation censored at last clinic visit. Graft survival was defined as the time from transplantation to the date reported by clinician as return to dialysis or death censored (to include those that died with a functioning graft). The analyses were limited to the first 12 months post-transplant. Primary allograft failure was defined as the need for maintenance dialysis within 6 months post-KT without the graft functioning sufficiently to sustain the recipient's life.

Serum creatinine values at weeks 1, 2, 4, 6, 8, 12, 24, 36 and 52 post-KT were used to determine graft function. Graft function was calculated by the estimating the glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula (Malyszko et al., 2010).

Analyses of acute allograft rejection were restricted to biopsy-confirmed episodes (BPAR). Biopsies that were inconclusive were reviewed by the clinician for a confirmed diagnosis. Acute allograft rejection was limited to the first episode that occurred within 12 months post-transplant. Patients with less than 12 months of follow-up were included in the AR analyses up to the date of last clinic visit taken.

Adverse Events

Adverse events (ADEs) were restricted to immunosuppression related events that occurred in the first 12 months post-KT stratified *a priori* by CNI choice an reported by clinicians. ADEs include: latent viral reactivations – cytomegalovirus (CMV), BK virus, Epstein-Barr virus, herpes simplex virus; opportunistic infections – bacterial/fungal/protozoal/viral infections; HIV virological control; tumors/malignancies; post-transplant lymphoproliferative disorder (PTLD); new onset of diabetes (NODAT); and drug induced cytopenias. CMV prophylaxis with an antiviral agent (e.g. valganciclovir) was noted.

Analyses of CNI Efficacy

Patients were *a priori* stratified by the type of calcineurin inhibitor (ciclosporin or tacrolimus) received immediately post-KT and, for pharmacokinetic analyses, by their antiretroviral regimen (protease inhibitor [PI] containing vs. PI sparing). Clinical characteristics at the time of KT were described. The CNI doses were recorded for each patient and expressed relative to total body mass (in mg/kg/day).

CNI C_{trough} concentration analyses were carried out at the following *a priori* selected time points: 1, 2, 4, 6, 8, 12, 24, 36 and 52 weeks post-KT. CNI C_{trough} doses and concentrations were censored at: date of clinical event (BPAR); date CNI drug was discontinued or switched; date of death or date of last clinic visit up to 1 year post-KT.

Calcineurin inhibitor C_{trough} concentrations were taken as the concentration taken at 12- or 24-hours post-dose for twice and once daily regimens respectively. Where patients were taking extended interval CNI dosing (i.e. once every 2, 3, 7 days), the pre-dose concentration was considered the C_{trough}. CNI concentrations not taken pre-dose for extended interval dosing regimens were excluded from the analyses.

The first CNI C_{trough} concentration measured after initiating a dose post-KT was considered when no dose change prior to first measurement available up to 7 days post-KT. For the subsequent selected time points, the CNI C_{trough} concentration within 10 days (either side) of the specified dates was chosen for analyses. Where two or more concentrations were available, the first available result following the specified date was used (Oo et al., 2008).

All available CNI whole blood concentrations were downloaded from their electronic patient records; these measurements were assumed to be taken at 12- or 24-hours post-dose for twice and once daily dosed drugs, respectively, and thus representing C_{trough} concentrations. Where patients had been taking extended interval CNI dosing (i.e. once every 2, 3, 7 days), the pre-dose concentration was considered the C_{trough}. For these patients, the daily dose was calculated by dividing the single dose taken by the number of days preceding the C_{trough} concentration reported. Analysis of CNI doses and C_{trough} concentrations used the following time points: weeks 1, 2, 4, 6, 8, 12, 24, 36 and 52 post-KT. If no concentration was available for these time points, C_{trough} concentrations were carried forward for a maximum of 7 days in the first 3 months post-KT, and for a maximum of 21 days thereafter.

All available CD+ T cell counts were assessed for immunological response stratified *a priori* by CNI choice at KT. Further analyses comparing cART choice, induction therapy choice and experiencing BPAR at 1 year were also carried out. Analysis was performed at baseline, month 1, 2, 4, 6, and 12 post-KT. The measurement closest to these time points were used.

Statistical Analyses

Baseline characteristics were compared using Z-test (proportions), Wilcoxon ranksum test (medians) or T-tests (means). Overall patient and graft survival and cumulative incidence/hazard were estimated using Kaplan-Meier methods. In this analysis, patients were censored at the first episode of acute graft rejection or at the time of CNI switch, whichever came first. The logrank test was used to compare groups. Risk factors for the allograft rejection episode occurring in the first 12 months post-KT were identified with Cox proportional hazard regression analysis. Analyses of CNI doses and concentrations were censored at CNI and/or cART switch.

A multi-level mixed effect linear regression model was used to analyse repeated measures data, i.e renal graft function measured at weeks 1, 2, 4, 6, 8, 12, 24, 36, 52. This mixed effect model was performed to examine whether there was a significant difference ($p < 0.05$) in change of graft function from baseline to week 52 for patients taking ciclosporin compared to those taking tacrolimus. The association of CNI choice and the slopes of graft function versus time post-transplant were also examined using mixed-effect models allowing for a random intercept and slope. The analyses were performed using the *xtmixed* command in STATA (version 12.0). Graft function was expressed as eGFR calculated using the CKDEPI equation.

Study Assumptions and Confounding factors

Continued adherence to both immunosuppressant and antiretroviral drugs was assumed for this chapter's analyses.

As this was an observational study, the confounding factors listed below were identified.

1. CNI switch in the first year post-transplant
2. Induction therapy choice (monoclonal, polyclonal or high dose steroids only)
3. Variability in centre biopsy protocols and histopathology/clinician interpretation of biopsy results
4. Variability in the immunoassays used for CNI whole blood concentration monitoring
5. Variation in immunosuppressant drug maintenance therapy to include
    a. Steroid withdrawal post-KT (i.e. withdrawal at 1, 3 or 3+ months post-KT)
    b. Maintenance with mono, dual or triple immunosuppression therapy
    c. Withdrawal of mycophenolate or azathioprine as the second IS agent

6. Variation in therapeutic target CNI drug concentrations. To standardise the analyses, the following target ranges were used
    a. Ciclosporin: weeks 1 – 12, 200 – 350ng/ml; weeks 13 – 52, 100 – 250ng/ml
    b. Tacrolimus: weeks 1 – 12, 8 – 15ng/ml; weeks 13 – 52, 5 – 10ng/ml

These target ranges were guided by taking the lower and upper values used of the local protocols for kidney recipients considered of high immunological risk.

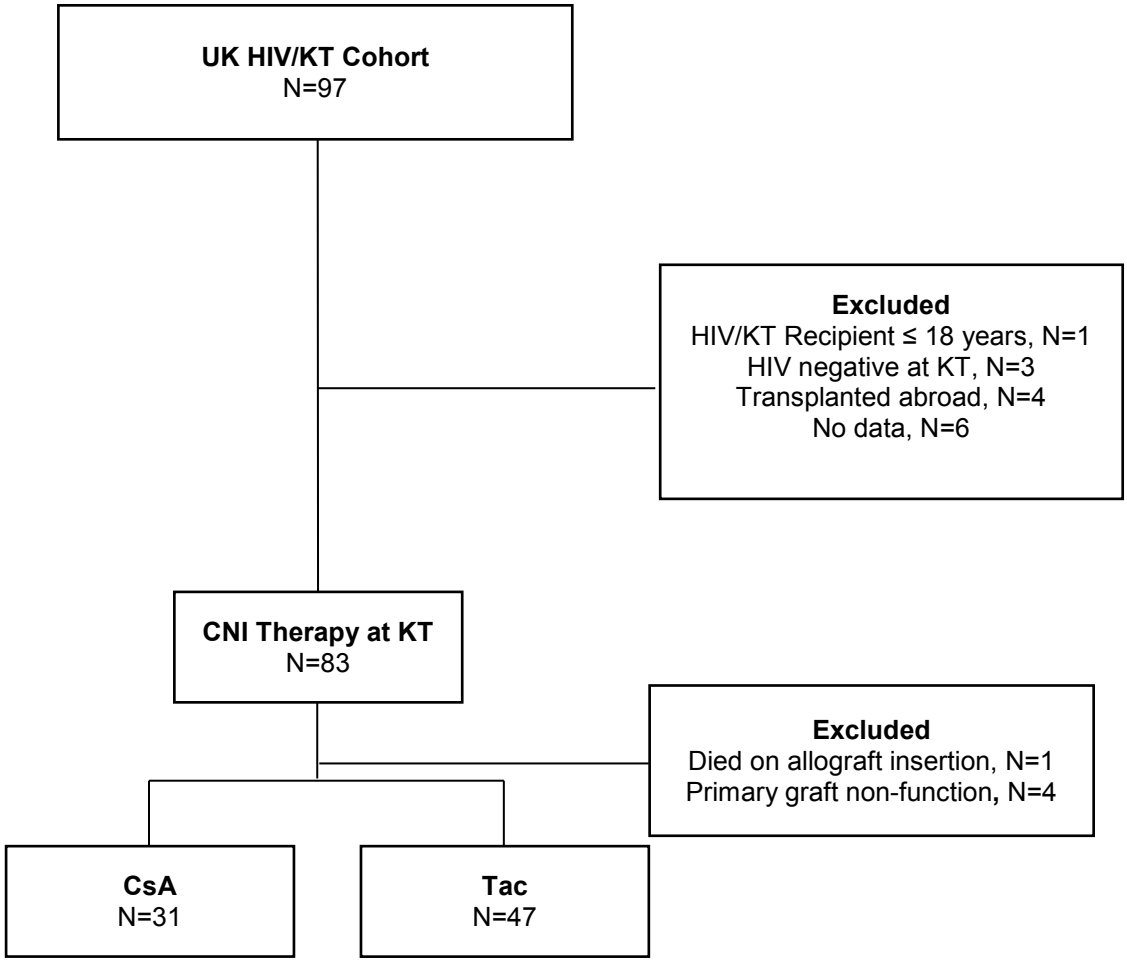
To control for confounding in the study design 1) patient characteristics at baseline in both CNI groups were tested for matching using paired statistical tests (e.g. t test or z-tests) (Austin, 2011), 2) patients were censored at CNI switch for time-to-event analyses (Velentgas, 2013). Other factors were not controlled for due to the study population size and intra- and inter-centre variability in IS protocols and immunoassays over the study period.

4.3. Results

Patient Disposition

There were 97 HIV positive adults that underwent kidney transplantation up until 31st December 2013 at the participating centres. Those that did not meet the study inclusion criteria (N=14) included: one patient less than 18 years of age; four transplanted abroad (India, Belgium, Berlin and USA); three that acquired HIV post-transplantation; one patient who died during KT and six that had no data. The six patients were transplanted at Oxford Radcliffe hospital (n=4), Birmingham (n=1) and Manchester (n=1). All were referrals from external HIV centers (unknown) and received post-transplant follow-up at their base hospitals.

Figure 22: Patient Disposition for UK HIV/KT Cases Stratified By Those on Ciclosporin and Tacrolimus Based Immunosuppression Therapy



Of the remaining 83 patients, 5 patients were further excluded one had died during allograft insertion and 4 experienced primary non-graft failure. The remaining 78 patients were included in the analyses, (see **Figure 22**).

Patient Characteristics

At KT, all recipient characteristics were well matched except for age, (see **Table 23**). The overall median (IQR) age of the patients was 44.6 (38.5, 51.4) years with those who received tacrolimus being older (median age 46.2 vs. 39.6 years, p=0.01) than those who received ciclosporin. The majority were male (67%) and of black ethnicity (74%) with a median (IQR) CD4 cell count of 366 (277, 516) cells/mm3 and well controlled HIV replication. Twenty-six patients (34%) received a kidney from a live donor, six (8%) were transplanted pre-emptively, one had received a previous kidney allograft 14 years earlier, one underwent simultaneous kidney-pancreas transplantation, one received an ABO incompatible graft, and one HCV co-infected recipient received two kidneys from an HCV positive donor. All of the patients were first time kidney transplant recipients; none were re-transplants. Hepatitis B and C co-infection was present in 13% and 5% respectively; hepatitis B DNA was undetectable in all hepatitis B positive patients while 2 of the 4 hepatitis C co-infected patients were viraemic (HCV RNA >700,000 IU/mL). Diabetes was present in 15% and hypertension in 90%. All except 3 patients contributed at least 12 months of follow up.

Table 23: **Baseline Patient Characteristics at Kidney Transplantation Stratified According to CNI Immunosuppression Therapy**

		All patients N=78	Ciclosporin N = 31	Tacrolimus N = 47	P value*
Recipient characteristics					
Age, median (IQR)	Years	44.6 (38.5, 51.4)	39.5 (36.6, 49.6)	47.3 (42.0, 52.6)	**0.01**
Gender, n (%)	Male	52 (67)	24 (77)	28 (60)	0.10
Ethnicity, n (%)	Black	58 (74)	24 (77)	34 (72)	0.62
Cause of ESKD, n (%) **	HIVAN	40 (52)	18 (58)	22 (48)	0.38
Duration of pRRT, median(IQR) ǂ	Years	4.9 (2.6, 7.1)	4.5 (2.2, 6.4)	6.1 (3.3,7.3)	0.27
HIV parameters, median(IQR)					
Mode of acquisition$^{\Psi}$, n(%)	HTS	54 (75)	22 (71)	32 (78)	0.46
Pre-KT nadir CD4 count†	Cells/mm^3	92 (40, 171)	92 (38, 160)	95 (41, 179)	0.93
CD4 count at KT**	Cells/mm^3	366 (277, 516)	398 (277, 601)	344 (276, 504)	0.28
Viral load	log10 copies/ml	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.6 (1.6, 1.7)	0.07
Co-morbidities, n (%)					
Diabetes		12 (15)	4 (13)	8 (17)	0.62
Hypertension		70 (91)	29 (94)	41 (87)	0.37
Hepatitis B co-infection, n (%)**		10 (13)	5 (16)	5 (11)	0.50
Hepatitis C co-infection, n (%)¶		4 (5)	3 (10)	1 (2)	0.16
Graft characteristics					
Allograft type, n (%)**	Cadaveric	51 (66)	18 (58)	33 (72)	0.21
HLA mismatch, median(IQR) ₹		3 (2, 3)	3 (2, 3)	3 (2, 4)	0.59
Donor/Recipient CMV mismatch status, n (%)	D+/R-	4 (5)	2 (6)	2 (4)	0.67
Antiretroviral drug therapy, n (%)					
PI/r containing		30 (38)	15 (48)	15 (32)	0.14
Lopinavir/ritonavir		12 (40)	9 (60)	3 (20)	
Darunavir/ritonavir		11 (37)	5 (33)	6 (40)	
NNRTI containing		40 (52)	15 (47)	25 (56)	0.14
Efavirenz		28 (67)	11 (73)	17 (63)	
Nevirapine		9 (21)	4 (27)	5 (19)	
Integrase inhibitor containing					
Raltegravir		23 (29)	8 (26)	16 (34)	0.45
Immunosuppressive therapy, n (%)					
Induction therapy[b]					
Basiliximab or Daclizumab		73 (94)	29 (94)	36 (92)	0.90
Alemtuzumab		2 (3)	0 (0)	2 (5)	
Rituximab+plasma exchange		1 (1)	0 (0)	1 (3)	
Pulsed corticosteroids only		2 (3)	2 (6)	0 (0)	
Triple IS regimen[a]		76 (97)	31 (100)	45 (96)	0.26
Tacrolimus monotherapy		2 (3)	-	2 (4)	

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test; comparing proportions (%), two-sided chi-squared test and two-sample test of proportions.

Statistically significant ($p < 0.05$); Missing values - **n=1, ¶ n=3, †n=5, Ψ n=6, ǂ n=7, ₹n=15, [b] Tacrolimus n=8.

Key: IS – immunosuppression, CNI – calcineurin inhibitor, HTS - heterosexual; [a]Calcineurin inhibitor + Mycophenolate or Azathioprine + corticosteroids

Antiretroviral Therapy

Overall at KT, 62% were being managed on a PI sparing cART regimen; 52% received a non-nucleoside reverse transcriptase inhibitor (NNRTI). In those on a PI containing cART regimen (38%) all took ritonavir boosted protease inhibitor (PI/r) containing ART. There were six patients that took a combination of NNRTI and PI/r containing ART regimens. Of those taking integrase inhibitor containing ART (n=23), only 10 patients took ART regimens that did not contain NNRTI or PI/r antiretroviral drugs.

Immunosuppressant Treatment Regimens

All patients received induction IS therapy with pulsed corticosteroids plus monoclonal antibodies (anti-CD25 [basiliximab or daclizumab, n=73], anti-CD52 [alemtuzumab, n=2], or anti-CD20 [rituximab, plus plasma exchange pre-conditioning for ABO-incompatibility, n=1]), or pulsed corticosteroids only (n=2). None of the patients received polyclonal anti-thymocyte globulin (ATG) as part of their induction regimen; 4 patients received ATG for anti-rejection treatment. All patients received a CNI as part of their initial post-KT immunosuppressive therapy; the initial CNI was ciclosporin in 31 and tacrolimus in 47 patients.

The majority of patients received triple immunosuppressive therapy with the CNI administered concurrently with mycophenolate (97%) and prednisolone (100%). There was between and within centre variability in corticosteroid withdrawal during the first 12 months post-KT (data not shown). During the first year post-KT, 16 patients (50%) discontinued ciclosporin (n=14 switched to tacrolimus, n=2 to sirolimus) after a median of 19.4 (IQR 11.4, 35.8) weeks, with reported reasons acute allograft rejection (n=11), incident Kaposi sarcoma (n=1), nausea (n=1), failing graft (n=1), CNI toxicity (n=1) and physician choice (n=1). Of those who initiated tacrolimus, one patient switched to sirolimus within 6 days post-KT due to CNI toxicity.

Calcineurin inhibitor doses and drug concentrations achieved are described in Chapter 5 (see page 222).

Allograft Outcomes

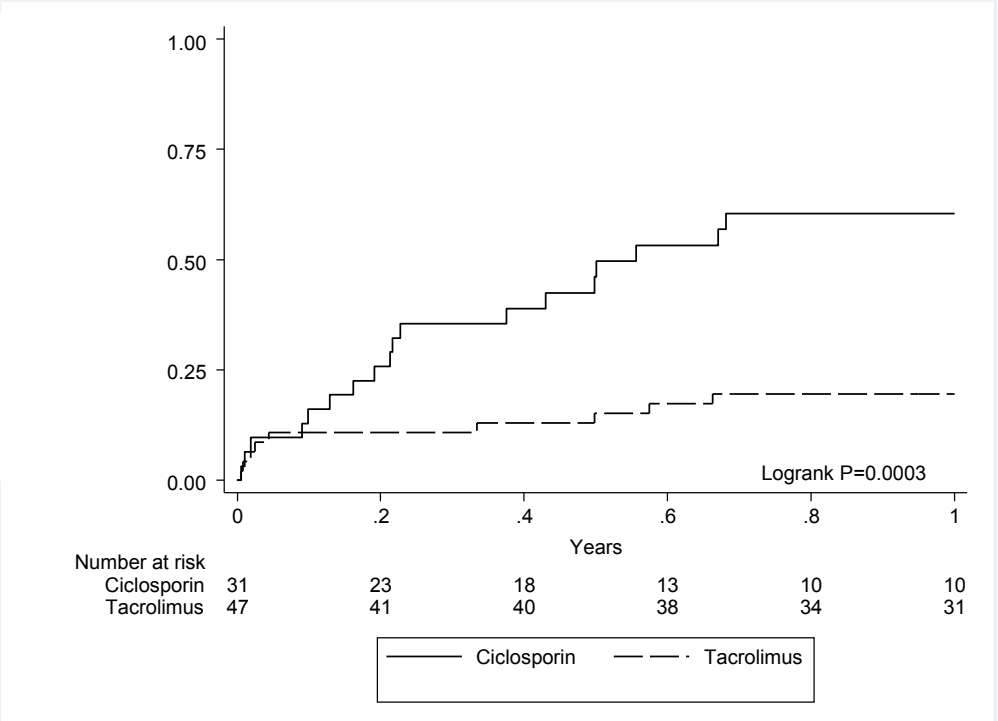
Delayed Graft Function

Delayed graft function occurred in 16 patients (21%; ciclosporin 7, tacrolimus 9) all of whom received an allograft from a deceased donor.In the first year post-KT, 2 patients died with a functioning graft, and 2 experienced complete graft failure due to AR. The overall 1 year patient and graft survival rates were 96.8% and 95.3% respectively.

Allograft Rejection

Acute allograft rejection was diagnosed in 28 (36%) patients. The median time to AR was 2.6 (0.5, 5.9) months from allograft insertion. Acute rejection was significantly more common among patients who started ciclosporin (n=18, 58%) compared with tacrolimus (n=10, 21%). At 1-year post KT, the cumulative incidence of acute rejection was 60% in the ciclosporin group compared with 20% in the tacrolimus group (p=0.0003, (see **Figure 23**). Nearly half of all AR episodes with tacrolimus occurred within 14 days of KT. By contrast, AR episodes with ciclosporin were common throughout the first 9 months post-KT.

Figure 23: Cumulative incidence of acute allograft rejection

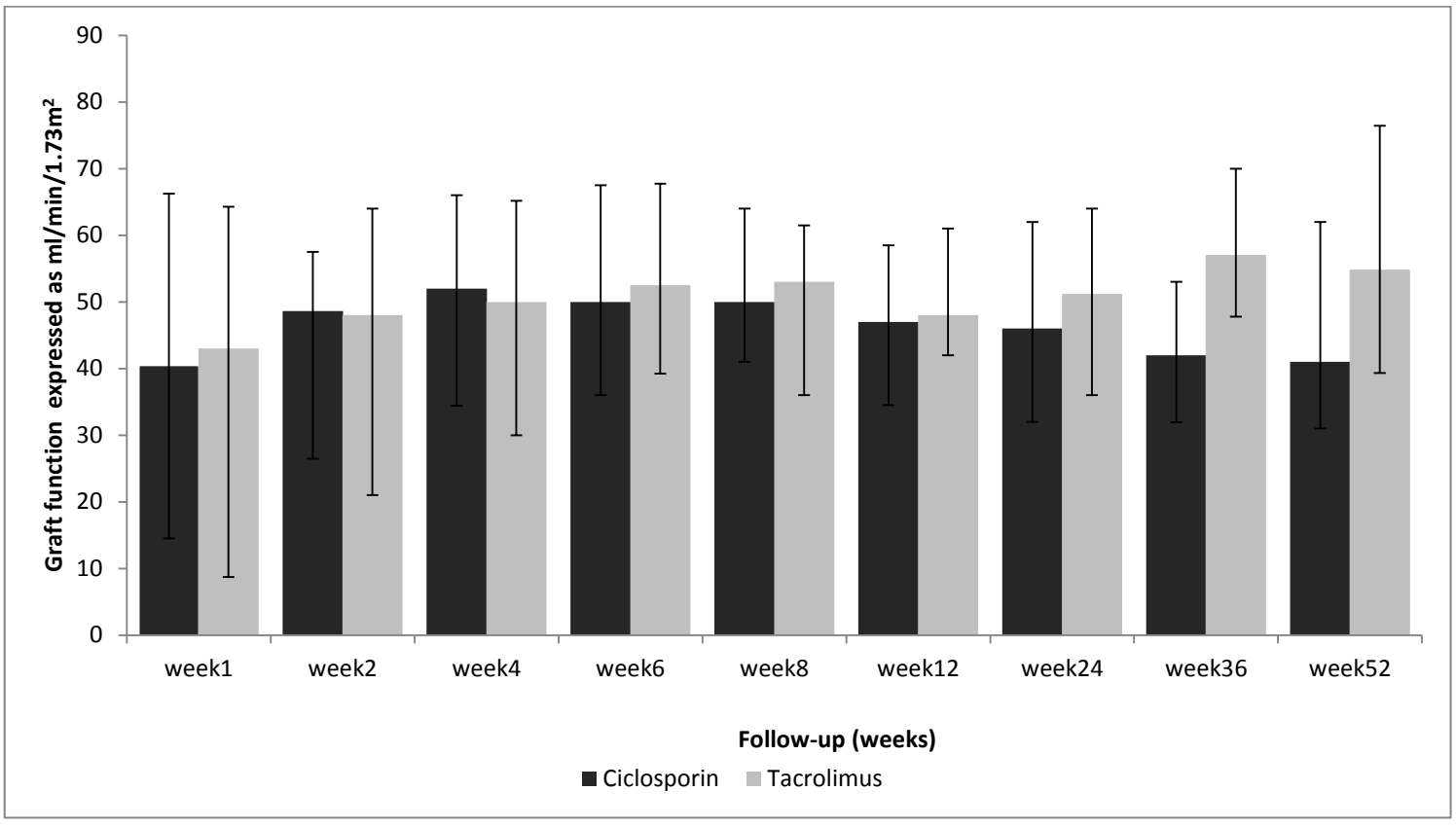


Data reflect time to first episode of acute allograft rejection (patients are censored at CNI switch).

Graft Function

The median eGFR at 52 weeks was 41 (IQR 31, 62) and 55 (IQR 40, 78) mL/min/1.73 m^2 for patients who initially received ciclosporin and tacrolimus, respectively, (see **Figure 24**). In a multi-level mixed effects model, eGFR at baseline was similar for both CNI groups with ciclosporin somewhat lower than tacrolimus (overall difference -2.92 (95CI -12.9, 7.1) ml/min/1.73^2, p=0.57). The rate of change in eGFR over the first year was significantly different in both groups (interaction p=0.000), with moderate decline observed in the Tac group (-0.09 (-0.20, 0.03)) and small increase in the ciclosporin group (0.25 (0.14, 0.36)). Findings were similar when last clinic visit was factored into the model with the rate of change in eGFR remaining significantly different between groups (interaction p=0.03). For patients that were taking tacrolimus, there was a modest decline of eGFR to last clinic visit (-0.03 (-0.055, -0.006) when compared to ciclosporin (0.01 (-0.02, 0.04)).

Figure 24: Post-Transplant Allograft Function



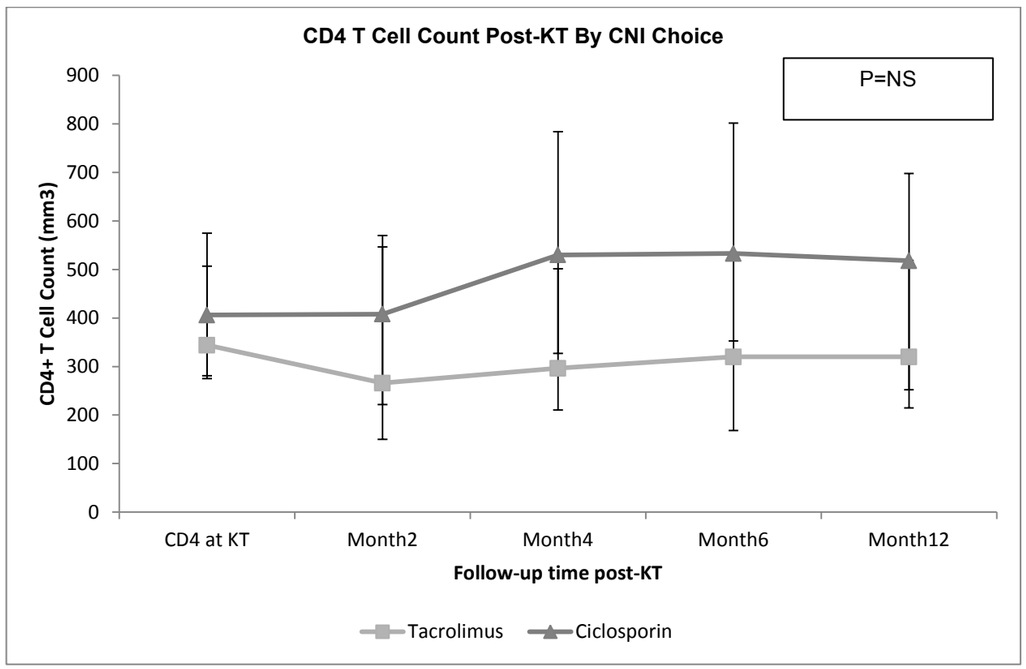
Graph showing graft function over the first year post-kidney transplant stratified by CNI choice. Graft function was defined by estimate glomerular filtration rate (eGFR) calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (Levey et al., 2009). Bars represented median eGFR and error bars the interquartile range.

Immunological Responses

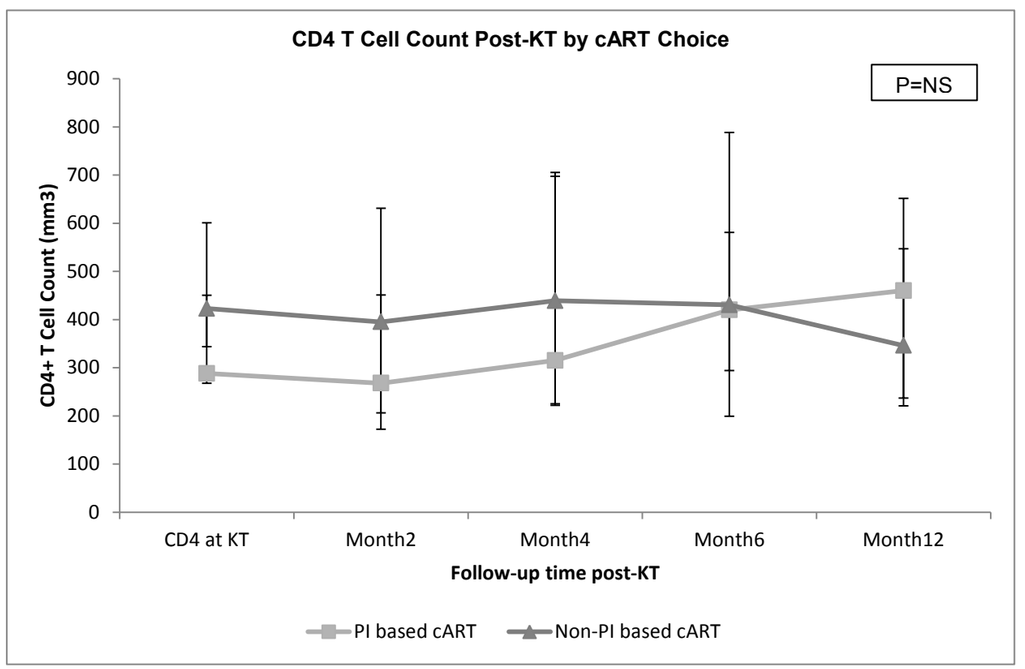
At baseline, there were no differences in the mean CD4 T cell counts in both tacrolimus and ciclosporin groups. Throughout the study period both groups maintained a CD4 T cell count > 200 cells/mm^3. In the ciclosporin group, recipients saw an increase and overall had higher CD4 T cell counts when compared to those on tacrolimus (see **Figure 25A**). The largest difference between the groups in CD4 T cell count was at month 4 and 6 although not significant p=0.05, p=0.11 respectively. When stratified by cART choice, no differences in CD4 T cell counts were found (see **Figure 25B**). When looking at choice of induction therapy, two patients on alemtuzumab (anti-CD52) showed significant persistent CD4 T cell depletion throughout 12 months of follow-up (see **Figure 25C**). Those that experienced AR seemed to have somewhat difference in CD4 T cell counts at 2 months post-KT compared to those that remained rejection free (see **Figure 25D**). Those on anti-CD25 therapies, basiliximab and daclizumab, maintained CD4 T cell counts >300 cells/mm^3 throughout the first year post-KT.

Figure 25: Changes in CD4+ T Cell Count Post-KT stratified by CNI choice

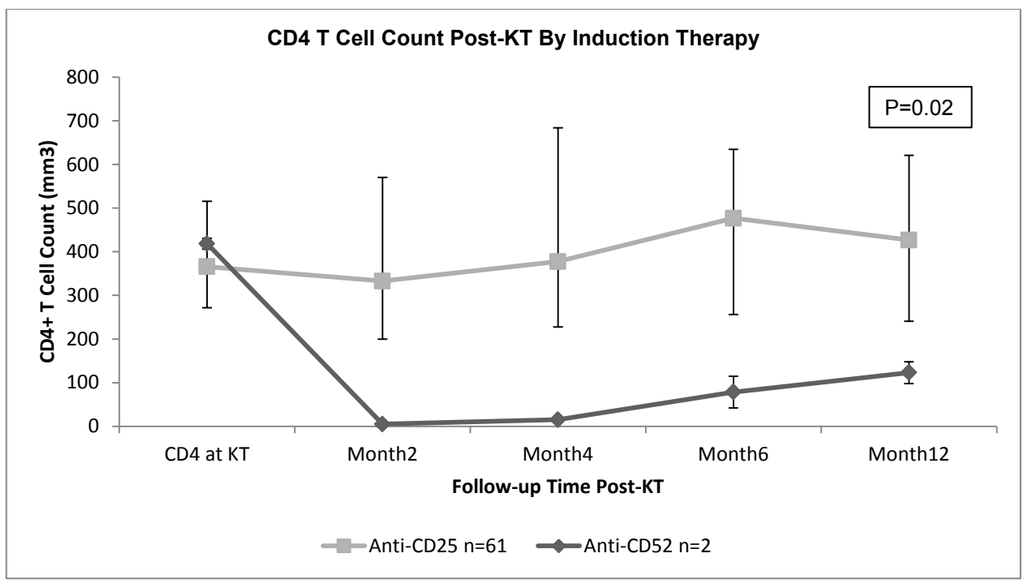
A. CNI choice at KT



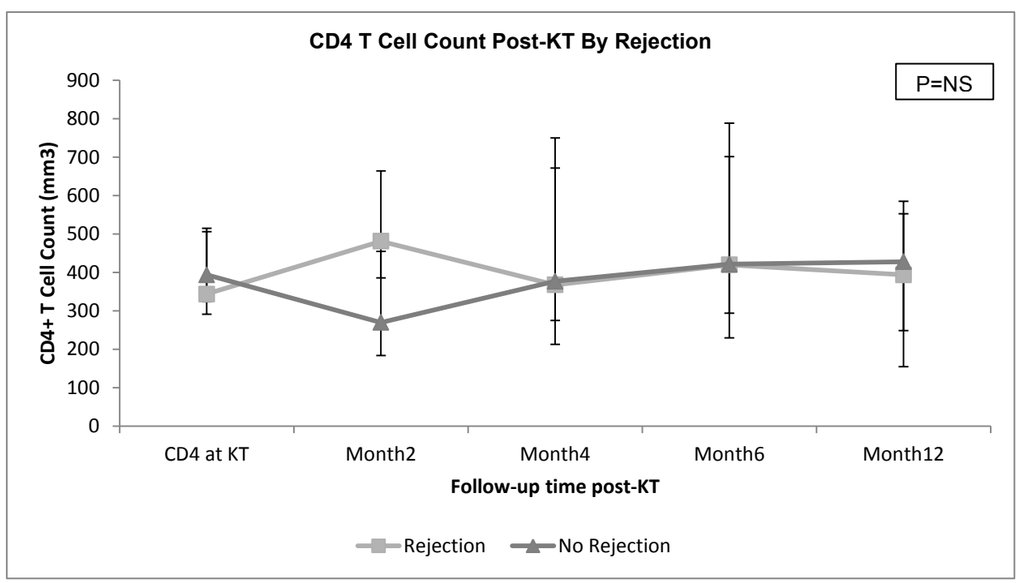
B. cART choice at KT



C. Induction Therapy Choice



D. Allograft Rejection

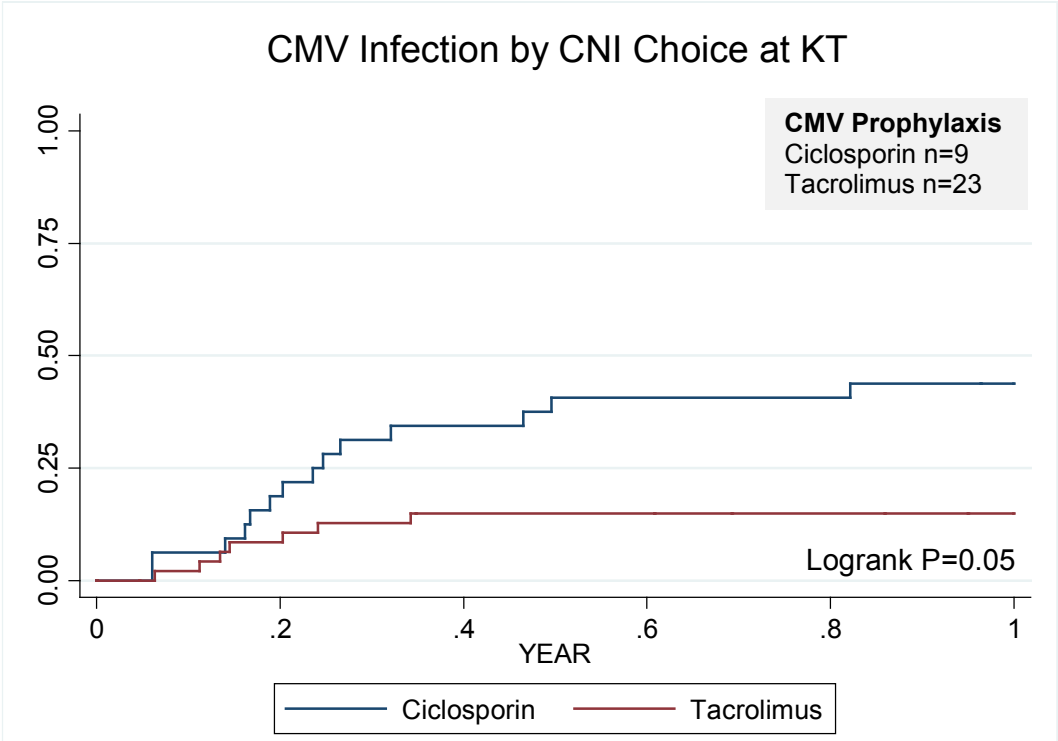


Graph of mean (SD) CD4+ T Cell Count change over time post-transplantation stratified by CNI choice (A), cART choice (B),choice of induction therapy (C) and allograft rejection (D). At baseline, patients on a non-PI had significantly higher CD4+ T Cell counts (ranksum p=0.02) although over time no differences were found between the two groups. Patients that received basiliximab and daclizumab, both antiCD25 monoclonal antibodies, had similar changes in CD4+ T Cell Counts during the follow-up period. There was one patient in our cohort on alemtuzumab (antiCD52) that showed significant CD4 T cell depletion that did not recover at 12 months post-KT.

CNI-associated Adverse Events

Reactivation of latent viral infections was more commonly observed in those taking ciclosporin compared to tacrolimus (overall n=22 vs. n=12 p=0.0002; cytomegalovirus (CMV) n=13 vs. n=7; herpes simplex (HSV) n=4 vs. n=2; Epstein-Barr Virus (EBV) n=0 vs. n=2; BK viraemia/nephropathy n=5 vs. n=1). However, primary CMV prophylaxis was less frequently prescribed in those who received ciclosporin (n=9) compared to tacrolimus (n=23) (p=0.02); (see **Figure 26**). CMV reactivation preceded AR in 9 of 12 patients, i.e. this was generally not precipitated by anti-AR therapy. HIV viral load blips <200 copies/ml occurred in four patients all taking CsA at KT, of whom three had latent viral reactivations. Those that had HIV viral load blips, three were on PI/r all of whom experienced an AR episode; the remaining patient on PI-sparing did not reject. There was no difference in the incidence of drug induced cytopenias (n=7 in each group). Two malignancies emerged (Kaposi sarcoma and lentiginous junctional melanoma, n=1 each), both patients on ciclosporin, and 2 cases of new onset of diabetes post-transplantation (NODAT), both in patients taking tacrolimus. One patient developed thrombotic microangiopathy while receiving tacrolimus.

Figure 26: Post-Transplant CMV Infection Stratified by CNI Choice at KT



Graph showing cumulative incidence of first CMV infection by CNI choice at KT over the initial 12 month period post-transplant

Factors Associated with Acute Rejection

Factors associated with rejection were analysed using Cox proportional hazard regression. Univariable analysis only identified one factor significantly associated with AR, the choice of initial CNI (hazard ratio [HR] for tacrolimus vs ciclosporin 0.25 [95% CI 0.11, 0.57], p=0.001). Recipient age, gender, ethnicity, deceased donor graft, year of KT, nadir or current CD4 cell count, and viral hepatitis status were not associated with AR, (see **Table 24**).

Six patients experienced allograft rejection within the first 2 weeks post-KT. These included antibody mediated rejection (n=4) and severe hyperacute rejection (n=2) episodes that would have occurred independent of CNI choice. Therefore, I performed a sensitivity analysis which included follow up from week 3 onwards, use of tacrolimus (HR 0.16 [95% CI 0.06, 0.43]) and abacavir (0.39 [95% CI 0.16, 0.94]) were protective whereas use of protease inhibitors (HR 2.63 [95% CI 1.08, 6.44]) was associated with an increased risk of AR. HLA-DR was the only immunological parameter assessed for the risk of developing rejection although, there was a proportion of patients with missing data (18%, n=14). Other immunological factors such as calculated reaction frequency (CRF) and re-transplantation were not tested in this cohort. Reasons for this include: changing clinical practice over the study changed from measuring panel reactive antibody (PRA) to CRF that prevented standardisation of the analyses; and, no patients had been re-transplanted, all were first time transplant recipients. Of these factors, only the use of tacrolimus (HR 0.19 [95% CI 0.06, 0.57]) remained significantly associated with a reduced risk of AR in multivariable analysis. Use of tacrolimus was not associated with AR in the first 2 weeks post KT (HR 0.88 [95% CI 0.20, 3.92]).

Table 24: **Factors Associated with Allograft Rejection in the First Year Post-KT**

Characteristics	Entire follow up (n=78)		Excludes follow up during the first 2 weeks post-KT (n=72)			
	Univariable		Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at KT (per year older)	1.00 (0.95, 1.04)	0.84	0.99 (0.94, 1.05)	0.71		
Gender						
Male	1.49 (0.63, 3.53)	0.36	1.58 (0.57, 4.34)	0.38		
Female	1.00		1.00			
Ethnicity						
Black	1.36 (0.55, 3.37)	0.51	0.92 (0.36, 2.41)	0.87		
Other	1.00		1.00			
Mode of acquisitionΨ						
Heterosexual	1.00		1.00			
Other	1.24 (0.55, 2.85)	0.60	1.61 (0.64, 4.05)	0.31		
Transplant year	1.04 (0.89, 1.21)	0.59	1.00 (0.84, 1.18)	0.97		
CD4 count at KT** (per 50 cell increase)	0.98 (0.89, 1.08)	0.71	0.98 (0.89, 1.08)	0.71		
HBV**						
No	1.00		1.00			
Yes	1.71 (0.65, 4.56)	0.28	1.97 (0.65, 5.93)	0.23		
HCV¶						
No	1.00		1.00			
Yes	2.80 (0.84, 9.38)	0.09	2.60 (0.60, 11.31)	0.20		
Recipient CMV IgG						
Negative	1.00		1.00			
Positive	0.83 (0.25, 2.78)	0.76	0.58 (0.17, 2.00)	0.39		
Not Tested	1.04 (0.21, 5.16)	0.96	0.68 (0.11, 4.10)	0.68		
Donor CMV IgG						
Negative	1.00		1.00			
Positive	0.92 (0.41, 2.09)	0.85	0.91 (0.35, 2.36)	0.85		
Not Tested	0.26 (0.08, 0.81)	0.02	0.24 (0.07, 0.90)	**0.04**		
Donor/Recipient CMV IgG mismatch						
D+R-	0.88 (0.12, 6.46)	0.90	1.00			
Other	1.00		1.26 (0.17, 9.41)	0.82		
HLA-DR Mismatch						
0	1.00		1.00		1.00	
1	0.99 (0.433, 2.56)	0.98	0.94 (0.37, 2.39)	0.90	1.26 (0.48, 3.28)	0.64
2	1.36 (0.30, 6.20)	0.69	1.75 (0.37, 8.25)	0.48	1.46 (0.30, 7.11)	0.64
Unknown	0.28 (0.06, 1.28)	0.10	0.17 (0.02, 1.34)	0.09	0.68 (0.07, 6.84)	0.74
CMV Prophylaxis						
Yes	1.35 (0.63, 2.9)	0.44	0.80 (0.31, 2.03	0.64		
No	1.00		1.00			
Allograft type¶						
Cadaveric	0.98 (0.44, 2.19)	0.96	0.72 (0.30, 1.77)	0.48		
Living	1.00		1.00			
Delayed graft function						
Yes	1.83 (0.80, 4.18)	0.15	1.50 (0.54, 4.13)	0.43		
No	1.00		1.00			
cART regimen						
PI/r	1.57 (0.74, 3.35)	0.24	2.63 (1.08, 6.44)	**0.03**	1.35 (0.52, 3.49)	0.54
Other	1.00		1.00		1.00	
Abacavir containing cART						
Yes	0.62 (0.29, 1.33)	0.22	0.39 (0.16, 0.94)	**0.04**	0.60 (0.24, 1.49)	0.27
No	1.00		1.00		1.00	
CNI Choice at KT						
Ciclosporin	1.00		1.00		1.00	
Tacrolimus	0.25 (0.11, 0.57)	**0.001**	0.16 (0.06, 0.43)	**0.000**	0.19 (0.06, 0.57)	**0.003**

HR=Hazard ratio estimated from Cox proportional hazard regression model with 95CI of the estimated HR. Model adjusted for CNI switch; CI=Confidence Interval; P=p-value;
Missing values - **n=1, ¶ n=3, Ψ n=6, [b] Tacrolimus n=8

4.4. Discussion

In this national observational cohort study of KT in HIV positive patients, acute allograft rejection was a frequent complication almost twice the rate seen in the general population (36% vs 12-24% respectively (Summers et al., 2010, Summers et al., 2013)). Overall, there was a significantly higher incidence of AR observed in the ciclosporin group compared to those that received tacrolimus (60% vs 20% at 1 year, p=0.0003). This rejects the null hypothesis. This was also proven in the multivariable analyses (Tacrolimus vs Ciclosporin HR 95CI: 0.27 (0.12, 0.61), p=0.002).

CNI Choice

In our cohort except for age, both CNI groups were well matched at KT; this included the choice of induction therapy which mainly consisted of anti-CD25 monoclonal antibodies plus pulsed corticosteroids. Maintenance therapy included a choice of CNI plus mycophenolate or azathioprine plus corticosteroids. This allowed for a comparison of ciclosporin versus tacrolimus based IS therapy in the management of HIV/KT. Results revealed a two-fold greater incidence of AR was observed with ciclosporin. This is consistent with data from the USA HIV/KT NIH study where the use of ciclosporin was associated with 2.1 (95% CI 1.1-3.9) fold increased risk of AR (Stock et al., 2010a). Although in their analysis, there was a proportion of patients not taking calcineurin inhibitor based IS therapy; of 150 HIV/KT patients in the study, 99 were on CsA, 33 on Tac and 18 on other immunosuppression therapy. Inferences could not be drawn from other HIV/KT cohorts as majority were small case series. In a small American cohort (N=40), all patients received ciclosporin plus sirolimus; allograft rejection occurred in 9 (22%) of recipients (Kumar et al., 2005). In a small Spanish case series (N=7), all patients were

taking tacrolimus based IS therapy of whom 40% (2/5) experienced allograft rejection; excluding 2 that lost their grafts within first week post-KT (Gomez et al., 2013). Another case series including 13 HIV/KT recipients in Italy observed 63% (5/8) AR rate in the CsA group and 60% (3/5) in the Tac group (Bossini et al., 2014). However in the Italian cohort, all recipients were on a steroid free IS regimen. The Parisian experience of HIV/KT (n=27; CsA n=11, Tac n=16) observed overall low rejection rate of 15% (n=4) (Touzot et al., 2010). The authors did not report which regimen the patients were taking but did conclude that the low rejection rate observed was due to the predominant use of Tac. In a recent report on the Portuguese experience of HIV/KT (n=17), all recipients were taking Tac and five experienced allograft rejection (Querido et al., 2015).

In the general population, tacrolimus has demonstrated more favourable outcomes post-kidney transplantation when compared to ciclosporin. A meta-analysis and meta-regression of early clinical trials between 1966 to 2003 identified 123 reports including 30 RCTs that examined the use of Tac compared to CsA for the post-transplant management of KT recipients (Webster et al., 2005). This analysis included a combined total of 4102 randomised kidney transplant participants from 30 RCTs. All primary post-KT outcomes favoured Tac over CsA. There was a significant reduction in allograft rejection by Tac at any time point post-KT especially at 6 months where there was a 55% marked reduction in AR by Tac compared to CsA, RR 0.45, 95%CI 0.33 to 0.60. Authors concluded that when Tac was selected over CsA, allograft rejection was avoided in 12 patients for every 100 kidney transplants performed.

In the past decade, studies have continued to resonate Tac being the more preferred CNI choice in kidney transplantation. The Symphony trial was such an example that demonstrated that low dose Tac to be highly efficacious compared to standard dose ciclosporin, low dose ciclosporin, and low dose sirolimus observed respectively a 12% (30/249), 26 % (61/233), 24% (60/248), and 37% (84/228) rejection rate at 1 year (Ekberg et al., 2009a). Although this was a pivotal study that instigated the use of low dose CNIs, the study outcomes were not generalizable to recipients with immunological high risk of allograft rejection. Clinical trials that examined the choice of CNI for patients at high risk of allograft rejection also found tacrolimus to be superior to ciclosporin. Especially in patients with steroid resistant allograft rejection or rejection that was recalcitrant to conventional therapy; Tac was more potent compared to CsA with reversibility of AR observed in > 70% of cases (Jordan et al., 1994, Eberhard et al., 1996, Woodle et al., 1996, Mayer et al., 1997, Hauser and Neumayer, 1998, Manu et al., 1999).

CNI Exposure & Allograft Rejection

It is possible that subtherapeutic CNI exposure contributed to the high rate of AR, refer to Chapter 5 for further analyses of CNI drug concentrations. Although C_{trough} concentrations are routinely used in clinical practice to guide CNI dosing, it is unclear how well C_{trough} concentrations correlate with total exposure (area under the concentration time curve [AUC]) in the HIV/KT population. Frassetto et al. recently reported that tacrolimus AUC correlated best with C_{trough} concentrations but that ciclosporin AUC showed better correlation with concentrations obtained at 4 hours post-dose (C_4 concentrations) (Frassetto et al., 2014). Interestingly, despite achieving higher proportions of therapeutic/supratherapeutic C_{trough} concentrations in the early period post-KT

we observed a higher proportion of AR episodes in the CsA/PI group compared to the CsA/PI-sparing group. This was not the case for those on tacrolimus where majority of those that had an AR episode were on PI-sparing regimens. Although not significant, there was somewhat higher proportion of patients that experienced an AR episode in the supratherapeutic group compared to the other groups (therapeutic and subtherapeutic).

When we analysed if the C_{trough} concentrations achieved at week 2 post-KT had an influence on AR, we found that having a supratherapeutic concentrations had a somewhat increased risk of AR compared to therapeutic or subtherapeutic concentrations (see **Figure 23**). Perhaps CNI overexposure causing nephrotoxicity could offer for a differential diagnosis. In the HIV negative population, clinical-pathological correlations have been sought to ensure correct diagnosis between CNI-induced nephrotoxicity and acute rejection (Liptak and Ivanyi, 2006). Exposure to high CNI concentrations may cause acute tubular necrosis (ATN), toxic tubulopathy or vascular toxicity while some forms of allograft rejection are also known to cause ATN type tubular damage (Liptak and Ivanyi, 2006).

Although, CNI concentrations have not been found to correlate well with kidney damage caused (Liptak and Ivanyi, 2006). Also irrespective of CNI concentrations, CNI metabolites have been known to cause nephrotoxicity. Frassetto et al (2013) performed pharmacokinetic studies of both ciclosporin and tacrolimus metabolites post-HIV/KT and found that patients on antiretroviral therapy with CYP enzyme inducing properties (e.g. NNRTIs, efavirenz or nevirapine), caused a profound increase in certain metabolites known to cause nephrotoxicity. By contrast, in the HIV negative population, low levels of certain metabolites e.g. AM1 and AM9 ciclosporin metabolites have been associated

with increased risk of allograft rejection (Bauer et al, 2003). Patients taking CYP enzyme inhibitor agents (e.g. protease inhibitors) although would increase the CsA drug concentrations, they have been found to reduce AM1 and AM9 (Frassetto, 2013) thus may increase risk of allograft rejection in this patient group.

When considering co-medication of antiretroviral drugs with CNIs, drugs such as tenofovir and atazanavir have nephrotoxic potential while others such as ritonavir- or cobicistat-boosted PI/integrase inhibitors may give rise to challenging drug-drug interactions (Yombi et al., 2014). In our analyses we see that the use of INI, raltegravir, to avoid drug interactions may be protective against allograft rejection. This was also observed in a French HIV/KT cohort that used raltegravir based cART (n=13) (Tricot et al., 2009a).

Other Factors Associated with Acute Rejection

In univariable analysis restricted to AR events that occurred 3-52 weeks post-KT, use of PI was associated with an increased risk of AR and use of abacavir with a reduced risk of AR. Ritonavir-boosted PI, through P-glycoprotein and CYP3A inhibition (Perloff et al., 2001, Kageyama et al., 2005), increase CNI exposure (2-4 fold for ciclosporin, 10 fold for tacrolimus) (Frassetto et al., 2013). Tacrolimus is particularly challenging to dose in patients receiving PI who required an approximately 100-fold dose reduction.

Abacavir is a guanosine analogue which may act synergistically with mycophenolate mofetil, a drug that blocks the formation of guanosine monophosphate, thus depleting the endogenous deoxyguanosine triphosphate (dGTP) pool (Margolis et al., 1999). Abacavir is phosphorylated to its active form carbovir triphosphate (CBVTP) which competes with endogenous dGTP

for incorporation into HIV viral DNA (Sankatsing et al., 2004a); mycophenolate may thus increase the antiviral efficacy of abacavir (Margolis et al., 1999). It is unknown whether abacavir enhances the immunosuppressive effects of mycophenolate. In multivariate analysis, however, the use of PI or abacavir was no longer associated with AR.

In univariable and multivariable analyses no association of CD4+ T cell count with allograft rejection was found. In the USA cohort, a higher CD4 T cell count was found to be marginally protective (hazard ratio per increase of 50 cells per cubic millimeter, 0.9; 95% CI, 0.9 to 1.0; P = 0.07) (Stock et al., 2010b).

Possible mechanisms of rejection in HIV/KT population

HIV/Ciclosporin Competitiveness for Cyclophillin

There are studies to demonstrate that HIV competes with ciclosporin for cyclophilin although the HIV/cyclophilin complex does not result in calcineurin inhibition as seen with ciclosporin (Luban et al., 1993). Some researchers suggest that calcineurin induces the activation of nuclear factor-kappa B (NFκB) which in turn stimulates the latent HIV long terminal repeat (LTR) (Chan et al., 2013). However, the inhibitory effect of CNIs is reversible and calcineurin recovery has been noted as early as 2 hours post-dose (Sommerer et al., 2009). Calcineurin recovery rates have noted to be quicker for ciclosporin compared to tacrolimus (Fukudo et al., 2005). Also, some research has shown that 50% of lymphocyte activity persists with ciclosporin permitting strong cytokine expression (Batiuk et al., 1995b). Furthermore, inhibition of p-glycoprotein transporters (responsible for the drug efflux), by protease inhibitors for example, that one would expect to result in increased intracellular ciclosporin

drug concentrations did not prevent the recovery of calcineurin activity in leukocytes (Batiuk et al., 1995b). This may provide some explanation for the AR episodes seen in the CsA/PI containing group of our study.

Enhanced Intracellular Efficacy of Tacrolimus

The advantage of using tacrolimus is that it binds to a different immunophilin, FKBP-12, that is highly expressed in lymphocytes (Marinec et al., 2008) unlike cyclophilin that is found in all cells (Wang and Heitman, 2005). This affinity for lymphocytes that have low levels of CYP3A4 enzymes provides for the prolonged half-life of Tac (Batiuk et al., 1995a). This effect has been explored to improve drug targeting and efficacy of protease inhibitors e.g. appending FKBP-binding portion of FK506 (tacrolimus) to amprenavir that resulted in a 20-fold improved half-life in mice (Marinec et al., 2008). This effect is probably what offers Tac a more efficacious profile compared to ciclosporin thus have fewer AR episodes.

HIV-driven Immunological Responses

Another explanation could be due to the immunological profile of HIV+ patients which differs to HIV negative patients. It has been noted that when HIV+ patients initiate antiretroviral therapy and CD4 T cell counts increase, the majority of these are memory T cells. It has been suggested that if these expanded T cells have cross-reactivity with alloantigens from the donor allograft; these cells may cause rejection (Stock et al., 2003b). Although this has yet to be elucidated in the HIV+ kidney transplant population.

There is also the possible B cell involvement where HIV+ patients are known to have HIV-associated B cell fatigue causing proinflammatory cytokine release that might prime antigen-presenting cells. This has been hypothesised in the HIV negative population where rituximab (antiCD20) monoclonal antibodies used for induction therapy causing B cell depletion that could be likened to B cell associated fatigue. This trial was stopped early due to the high rate of rejection, 83% vs 14% in the control group (n=13) (Clatworthy et al., 2009). Acute cellular rejection (ACR) was most commonly observed in this trial which has also been noted in HIV/KT recipients; 28% at 1 month and 55% at 12 months post-KT (Malat et al., 2012).

There is also the possibility of latent viral reactivations that infect the graft. In our cohort, we observed only 3 cases of BK nephropathy and no other viral caused nephropathies. In a French cohort that examined protocol biopsies post-HIV/KT found HIV infected the transplanted allograft in 68% of patients (n=19) despite well controlled HIV (undetectable HIV RNA in plasma < 50cps/ml). HIV was predominantly detected in the podocytes that resulted in a rapid decline in allograft function compared to those with tubular cell infection (Canaud et al., 2014).

The strength of this study is near complete sample that was well matched allowing for controlling of confouding factors. Also, detailed data were available on HIV treatment, IS management (including drug concentrations), CD4 cell counts and HIV viral loads. Nonetheless, the study has several limitations including its observational nature, the non-standardised KT protocols employed

at the participating centres with evolution over the 8 year study period, the relatively small number of patients, retrospective case identification, and some missing data. Whilst we assumed available drug concentrations to reflect C_{trough} concentrations, we were unable to ascertain which of those reported drug concentrations were true C_{trough} concentrations. Chapter 5 contains further analyses of CNI drug concentrations. There were clinical parameters not measured in this study that may have useful in the analyses of allograft rejection including pre-transplant calculated reaction frequency (CRF)and post-transplant donor specific antibodies. These parameters may have enabled in the identification of immunologically high risk HIV/KT patients.

4.5. Conclusion

The results support the hypothesis that HIV positive kidney transplant recipients receiving ciclosporin based immunosuppression therapy have higher allograft rejection rates in the first year post year post-transplant compared to tacrolimus based IS therapy. This suggests that tacrolimus may be the preferred choice for the management of HIV kidney transplant recipients. This finding is consistent with data from the general KT population and emerging data from HIV positive patients.

Chapter 5. Achieving Therapeutic Drug Concentrations in HIV+ Kidney Transplant Recipients

5.1. Introduction

Calcineurin inhibitors, ciclosporin and tacrolimus, have a narrow therapeutic index which requires close therapeutic drug monitoring (Schiff et al., 2007). This makes CNI dosing and achieving therapeutic drug concentrations quite challenging particularly during the early period post-transplant when immunosuppression drug management is critical (Perico et al., 2004). Not achieving and maintaining therapeutic drug concentrations throughout the life of the host/graft is detrimental for short and long-term transplant outcomes (Perico et al., 2004, Gotti et al., 2005, O'Seaghdha et al., 2009). Although there are many factors that cause variations in CNI drug exposure to include: drug formulation (Hibberd et al., 2006, Qazi et al., 2006, Sharma et al., 2006); food (Takeda et al., 2007) or drug interactions (van Maarseveen et al., 2012); gender (Min et al., 2000); pharmacogenetics (Macphee et al., 2002, MacPhee, 2012); or patient adherence (Borra et al., 2010a). Furthermore, haemodynamic changes in the patient post-transplantation may also contribute to the changes in CNI drug exposure (Capela et al., 2014). The resulting inter- and intra-patient variability CNI drug concentrations have been known to put kidney transplant recipients at risk of allograft rejection and subsequently reduced graft survival (Borra et al., 2010a). By contrast, CNI over-exposure puts kidney transplant recipients at risk of adverse drug reactions to include nephrotoxicity (Scholten et al., 2005).

Within the HIV positive population achieving the optimum immunosuppression is vital, not only for the prevention of allograft rejection but also, for the prevention of morbidity and mortality which includes reactivation of latent viral infections (Palefsky and Holly, 2003). Opportunistic infections can accelerate the progression of HIV disease (Nelson et al., 2011) therefore, preventing latent viral reactivation in immunocompromised patients through achieving the right balance of immunosuppression is crucial. Furthermore, HIV positive patients take antiretroviral drugs that share the same metabolic and transporter pathways as calcineurin inhibitor immunosuppressant drugs resulting in profound drug-drug interactions (van Maarseveen and van Zuilen, 2013). These drug interactions make achieving and maintaining the 'therapeutic' window of the calcineurin inhibitor drugs challenging in clinical practice.

Metabolism of Calcineurin Inhibitors

Ciclosporin

Ciclosporin is highly lipophilic which results in variation in the oral bioavailability of between 1 to 89%. The first formulation of CsA, Sandimmune ®, was oil based which limited aqueous solubility resulting in poor oral absorption. Neoral ® was later introduced using a new formulation where a microemulsion formed on contact with water. This somewhat improved oral absorption, particularly via the small intestine, however, there was still a wide inter- and intra-patient variability (Knops et al., 2013).

Once ciclosporin is absorbed, almost half is metabolised in the intestine and 8% is lost to first pass hepatic metabolism. The remainder is distributed to the plasma (33 to 47%), lymphocytes (4 to 9%), granulocytes (4 to 12%) and erythrocytes (41 to 58%). The percentage available in the plasma is highly protein bound (98%). Ciclosporin is a substrate for the multidrug resistance protein (MRP) p-glycoprotein transporter and is primarily metabolised by cytochrome P450 3A4 isoenzymes (**Table 25**)(Knops et al., 2013). This metabolic pathway subjects CsA to multiple drug interactions. The biotransformation of CsA produces 30 metabolites which have different activity. For example, AM1 metabolite can inhibit T cell function (Ozbay et al., 2007).

Table 25: Summary of Metabolism and Transporter Mechanisms of Commonly Used Immunosuppressant Drugs in Kidney Transplantation

Immunosuppressant Drug Metabolism (ASHP, 2015, PharmGKB, 2015)		
	Metabolised by	**Transported by**
Calcineurin Inhibitors		
Ciclosporin	CYP3A4, CYP3A5	P-gp, MRP-1
Tacrolimus	CYP 3A4, CYP 3A5	P-gp
mTOR Inhibitors		
Sirolimus	CYP3A4, CYP3A5, UGT1A8	P-gp
Everolimus	CYP3A4, CYP3A5, 2C8	P-gp
Antiproliferative/Corticosteroids		
Azathioprine	TPMT, HGPRT	-
Mycophenolate	UGT	MRP-2
Prednisolone	CYP3A4	P-gp, MRP-1

Key:
CYP, cytochrome P450; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; MRP, multi-drug resistance protein; P-gp, P-glycoprotein; TPMT, Thiopurine-S-methyltransferase; UGT, UDP-glucuronosyltransferase

Tacrolimus

Similarly to ciclosporin, tacrolimus exhibits poor oral bioavailability which is further reduced by the ingestion of fatty meals with only approximately 20% reaches the systemic circulation after oral administration. This results in a wide intra-patient variability ranging from 4 to 93% (Knops et al., 2013). Alterations in gut motility and the presence of loose stool have been found to influence the absorption of tacrolimus (Hochleitner et al., 2001, Nakamura et al., 2014). Furthermore, HIV associated enteropathy, involving damage to the gastrointestinal epithelial layer, villous atrophy, crypt hyperplasia and villous blunting; may reduce enzymatic activity in the small intestine thus influencing plasma concentrations (Mittal et al., 2001, Brenchley and Douek, 2008). Once tacrolimus reaches the circulation, only 5% is distributed into the plasma compartment, the majority being bound in erythrocytes (Knops et al., 2013).

Tacrolimus is a substrate for p-glycoprotein and is primarily metabolised by cytochrome P450 3A4 and 3A5 isoenzymes (refer to **Table 25**). Nine metabolites have been identified to date and 4 have been found to have potent immunosuppressant activity. CYP3A5 is more influential in the metabolism of tacrolimus and genetic polymorphisms have been demonstrated to guide the dose requirements in particular patient groups. For example, patients of black ethnicity possessing the CYP3AP1 G allele are known to be high expressers of 3A5 and therefore require higher tacrolimus doses compared to other ethnic groups (Macphee et al., 2002, MacPhee, 2012). In addition, physiological changes that occur post-transplant may alter the requirements of tacrolimus. For example, the use of anaesthesia and accompanied dehydration post-KT could result in

decreased intestinal motility which may in turn increase metabolism and/or tacrolimus absorption in the small intestine. This is important to consider as some of the antiretroviral drugs are known to cause diarrhoea (MacArthur and DuPont, 2012) that could affect the absorption of tacrolimus. Alterations to P-gp and CYP3A4 activity post-transplantation associated with changes to gut microbiota following the use of antibiotics, gastric acid suppressants and corticosteroid tapering, could also influence the tacrolimus dosing regimen (Lemahieu et al., 2005a, Lemahieu et al., 2005b, Lee et al., 2015).

CNI and Antiretroviral Drug Interactions

Antiretroviral drugs that share transporter and metabolic pathways with calcineurin inhibitors are subject to drug-drug interactions. Transporter proteins and metabolic enzymes responsible for the handling of antiretroviral drugs currently available in the UK are summarised in **Table 26**. Overall, there are two major classes of ARVs that demonstrate clinically significant pharmacokinetic drug interactions, non-nucleoside reverse transcriptase inhibitors, which are inducers of p-glycoprotein and cytochrome P450 enzymes, and protease inhibitors which are potent P-gp and CYP enzyme inhibitors. The use of P-gp or CYP3A4 inhibitors would extend the elimination half-life of immunosuppressants thus alter the time it takes to achieve steady state and, depending on dosing frequency, the maximum whole blood concentration (C_{max}) and total exposure (AUC) achieved (Venkataramanan et al., 1995). Additionally, depending on drug concentrations, the kinetic order could change from first order to zero order kinetics (Rowland et al., 2011).

There are several approaches to managing the extension of the drug elimination half-life, such as:

a. Administer a loading dose
b. Extend the dosing interval
c. Reduce the dose given

When managing pharmacokinetic drug interactions several strategies could be utilised pre-emptively in order to avoid sub- or supra-therapeutic drug concentrations. There are multiple influential factors to consider e.g. drug half-life, liver/renal impairment, absorption, enterohepatic recycling, distribution, metabolism, excretion, protein binding. Both ciclosporin and tacrolimus are highly protein bound, 90 to 98% respectively, and when absorbed less than 1% is excreted in the urine. With so little excreted via the kidneys, no dose adjustment is required in renal impairment (Ashley and Dunleavy, 2014). The half-life of both CsA and Tac ranges from 5 to 20 hours and 12 to 16 hours respectively. Therefore, it could take between 1 to 4 days for CsA/Tac to reach steady state whole blood concentrations. However, this does not take into account that the drug half-life could be further altered by drug interactions as well as haemodynamic or metabolic changes that occur post-transplantation (Venkataramanan et al., 1995, Schiff et al., 2007, Frassetto et al., 2013).

Co-administration of ciclosporin or tacrolimus with either NNRTIs or PIs would require a CNI dose increase and decrease respectively (see **Table 27**). Other antiretroviral drug classes are unlikely to interact therefore, minimal or no CNI dose adjustments would be expected (van Maarseveen et al., 2012, LHPG, 2015).

CNI Therapeutic Drug Monitoring

Ciclosporin and tacrolimus both possess narrow therapeutic indices that require routine therapeutic drug monitoring (TDM) which determine drug efficacy and toxicity. Total drug exposure, determined by the area under the whole blood concentration-time curve (AUC), would be the ideal parameter to use for TDM however; it is not practical in clinical practice. For these reasons, limited sampling strategies have been found more attractive in routine clinical care. However, there is conflicting evidence of the optimal time point for CNI TDM. Early studies on ciclosporin TDM demonstrated better correlation of the maximum concentration ($C_{max)}$ and AUC with allograft rejection compared to the pre-dose concentrations (C_{trough}) (Kasiske et al., 1988, Schiff et al., 2007). Although, monitoring C_{max} and AUC in routine clinical care was also not feasible due to the inaccuracies of sampling times. Monitoring both C_{trough} and C_{max} at 2 hours post-dose (C_2) was later found to best correlate with total CsA exposure (AUC) to avoid allograft rejection (Keown et al., 1996, Levy et al., 2002, Schiff et al., 2007). It was the Concert research group (Levy et al., 2002) that reiterated that C_2 monitoring was the optimal time point for CsA TDM and that C_{trough} poorly predicted clinical events. However, the Concert group also noted that there were patients that were poor or slow absorbers of CsA which meant that C_2 was not representative of Cmax for all patients. It was also argued, that the use of adjunctive immunosuppressant drug therapy, such as mycophenolate, or induction therapy would reduce the need to monitor C_2 concentrationsalthough there wasn't strong evidence to support this (Hardinger et al., 2004c, Remuzzi et al., 2004). Consequently, single point monitoring of C_{trough} became routine clinical practice.

Aside from the sampling time, achieving therapeutic concentrations in the immediate period post-transplant was crucial. In the general population, there were studies that demonstrated achieving either therapeutic C_2 or C_{max} CsA concentrations early, in the first 2 weeks post-transplantation, were a strong predictor of allograft rejection (Clase et al., 2002, Internation Neoral Renal Transplantation Study, 2002, Levy et al., 2002, Gotti et al., 2005, Schiff et al., 2007). However, there are other competing factors during this time period that could deter from achieving therapeutic concentrations such as delayed graft function and/or induction therapy choice (Clase et al., 2002, Hardinger et al., 2004c, Schiff et al., 2007).

By contrast, several studies showed that tacrolimus AUC best correlated with C_{trough} concentrations (Balbontin et al., 2003, Undre, 2003, Scholten et al., 2005, Schiff et al., 2007). However, some studies demonstrated that Tac whole blood concentrations drawn 4 hrs post dose were a better predictor of clinical events compared to C_{trough} concentrations (Wong et al., 2000, Armendariz et al., 2005, Schiff et al., 2007). Due to practical and cost-effective reasons as discussed previously, C_{trough} Tac monitoring has become the norm in clinical practice.

Table 26: Summary of Metabolism and Transporter Mechanisms of Antiretroviral Drugs

Antiretroviral Drug Metabolism (van Maarseveen et al., 2012, ASHP, 2015, LHPG, 2015)			
	Metabolised by*	**Transported by**	**Enzyme/Transporter Induction or Inhibition Effect**
Protease inhibitors (PI)			
Atazanavir	3A4	P-gp, MRPs, BCRP	Inducer of P-gp, MRP1 Inhibitor of 3A4, 2C8 UGT1A1, BCRP, P-gp, MRPs, OATP
Darunavir	3A4	P-gp	Inducer of 2C9, 2C19, 2C8 Inhibitor of 3A4, 2D6, P-gp, OATP
Fosamprenavir	3A4	P-gp	Inducer possibly 3A4 with ritonavir Inhibitor of 3A4, BCRP, P-gp, MRP1, OATP
Indinavir	3A4	P-gp, MRP1, MRP2, OATP	Inhibitor of 3A4, P-gp, MRP1, OATP-C
Lopinavir	3A	P-gp	Inhibitor of 3A, BCRP
Nelfinavir	3A, 2C19, 2C9, 2D6	P-gp, MRP1&2	Inhibitor of 3A, MRP1, BCRP, OATP-C
Ritonavir	3A, 2D6	P-gp, MRP1	Inhibitor of 3A, 2D6, P-gp, MRP1, OATP-C, BRCP Inducer of 1A2, 2C8/9/19 & MRP1.
Saquinavir	3A4	P-gp, MRP1&2, OATCP	Inhibitor of P-gp, MRP1, BCRP, OATP-C
Tipranavir	3A4	P-gp	Inhibitor of 3A4/5, 2D6, P-gp, BCRP. Inducer of 3A, P-gp, 2C19
Non-nucleoside reverse transcriptase inhibitors (NNRTI)			
Delavirdine	3A4, 2C9, 2D6, 2C19	BCRP, MRPs	Unknown
Efavirenz	3A4, 2B6	P-gp	Inducer of 3A4, 5, 7 Inhibitor of 2C9, 2C19&3A4
Etravirine	3A4, 2C9, 2C19 UGT	P-gp	Weak Inducer of 3A4 Weak inhibitor of 2C9, 2C19, P-gp
Nevirapine	3A4, 2B6	P-gp	Inducer of 3A4, 5, 7
Rilpivirine	3A, potential 2A19	Not significantly transported by P-gp	P-gp inhibitor; unlikely to induce or inhibit CYP enzymes at dose of 25mg daily
Integrase/Entry Inhibitors			
Dolutegravir	UGT1A1 with some 3A contribution; Substrate of UGT1A3, UGT1A9	BCRP and P-gp	Does not inhibit or induce CYP enzymes or transporters
Elvitegravir/cobicistat	Elvitegravir – 3A and UGT1A1 and UGT1A3; Cobicistat – 3A, 2D6 (minor)	P-gp primarily	Elvitegravir inducer of 2C9 and UGT (modest); Cobicistat inhibitor of 3A, 2D6, P-gp, BCRP, OATP1B1, OATP1B3
Maraviroc	3A4	P-gp	Unlikely to induce or inhibit at clinically relevant concentrations
Raltegravir	UGT1A1; no CYP450 involvement	Unknown	No CYP450 or P-gp inhibition or induction

*CYP450 enzyme unless indicated.

Key: BCRP, = breast cancer resistance protein; CYP, =cytochrome P450; MRP =multi-drug resistanceprotein; OATP= Organic anion-transporting polypeptide; P-gp = P-glycoprotein; UGT =UDP-glucuronosyltransferase

Table 27: Calcineurin Inhibitor and Antiretroviral Drug-Drug Interaction Table

Drug Interactions between CNIs and Antiretroviral Drugs (Buncherd et al., 2012)					
	NRTI	**NNRTI**	**PI**	**INI**	**MVC**
Calcineurin Inhibitors					
Ciclosporin	-	↓	↑↑↑	-	-
Tacrolimus	-	↓	↑↑↑	-	-
mTOR Inhibitors					
Sirolimus	-	↓	↑↑	-	-
Everolimus	-	↓	↑↑	-	-
Antimetabolite/Corticosteroids					
Azathioprine	-	-	-	-	-
Mycophenolate	↑*	-	-	-	-
Prednisolone	-	↓	↑	-	-

Key: (-), No interaction in literature or unexpected from theoretical metabolism/transporter mechanisms; ↑, increase in drug concentrations; ↓, decrease in drug concentrations; Number of arrows represents the degree of the interaction expected; ↑*, in vitro evidence of increase intracellular drug concentrations.

Summary of Published Evidence of DDIs between CNIs and ART Post-HIV/KT

Co-administration of calcineurin inhibitors with antiretroviral drugs particularly those with P-gp/CYP inhibition or induction properties makes achieving the optimal CNI dose post-kidney transplantation challenging. Reports in the literature, have described the need for CNI dose adjustments required in order to achieve therapeutic CNI drug concentrations in patients co-administered antiretroviral therapy. In summary, the co-administration of tacrolimus with P-gp/CYP inhibitors – 'PI containing cART' then a dose reduction up to 140 fold may be required (see **Table 28**). Ciclosporin dose reduction is also required when co-administered with PI-containing cART although to a lesser extent compared to Tac, ~20 fold. Modest dose adjustments are required when both Tac and CsA are co-administered with PI-sparing cART (see **Table 29**).

Although the literature summarises the CNI doses used when co-administered with cART, clinical studies have not been conducted to describe in clinical practice the following:

i. Distribution of C_{trough} concentrations throughout the first 12 months post-HIV/KT with proportion that achieved sub-, supra- and therapeutic C_{trough} concentrations
ii. Relationship of CNI dose and C_{trough} concentration achieved
iii. Time to achieve therapeutic CNI C_{trough} concentrations in the early period post-HIV/KT
iv. CNI doses used to achieve therapeutic CNI C_{trough} concentrations in the early period post-HIV/KT
v. Inter/Intrapatient variability of C_{trough} concentrations determined during periods of stability (6 to 12 months) post-transplant
vi. Factors associated with CNI C_{trough} concentration achieved and clinical end-points such as allograft rejection, graft function or graft loss

Table 28: Summary of Evidence (case studies, case series, prospective studies) of CNI and Drug Interactions with PI-Containing Antiretroviral Drug Therapy

PI Containing ART					
Publication	**Organ**	**N**	**ART Regimen**	**Effect on Dose**	**Effect on Pharmacokinetic parameters**
Ciclosporin					
(Brinkman et al., 1998)	KT	1	SQV	50% dose reduction	300% higher CsA AUC concentrations; SQV AUC 500% higher than 5 controls not taking CsA.
(Gruber et al., 2008a)	KT	8	PI/r Not specified	Dose ranges: • 25mg q 24h, q 48h • 50mg to 75mg q 12h • 75 q 72h • 125mg q 48h • 175mg q 72h	C_{trough} concentrations not reported; doses aimed at achieving C_{trough} concentrations of 225 to 300 ng/ml.
(Gregoor et al., 1999)	KT	1	SQV/r	50mg q 12h	Drug concentrations over 1000 ng/mL
Tacrolimus					
(Hardy et al., 2004)	KT	1	SQV/r	0.5mg once a week; 140-fold dose reduction	Drug concentrations over 175 ng/mL
(Tan et al., 2004a)	KT	3	Not specified	Case 1: 0.1mg q 96h Case 2: 4mg q 24h	C_{trough} concentrations:- Case 1: 3.7ng/ml Case2: 7.0ng/ml; Renal toxicity noted on biopsy.
(Frassetto et al., 2007)	KT & OLT	35 (20 KT, 15 OLT)	Not specified	80% dose reduction & 7 fold increase in dosing interval	Similar drug concentrations achieved to patients not on ART after dose adjustment.
(Sheikh et al., 1999)	KT	1	NFV	Dose ranged from 0.5mg q 24h to 4mg q 12h	C_{trough} concentrations ranged from 23.7 to > 120 ng/ml; Neurological toxicity
(Jain et al., 2003)	OLT & SLK	3	LPV/r	1 mg once a week	C_{trough} concentrations 2.9 to 5.4 ng/ml
(Mertz et al., 2009)	SPK	1	DRV/r	Dose reduction to 3.5% of normal dose	Drug concentrations over 100 ng/mL
(Morelle et al., 2010)	KT	1	LPV/r	0.5mg once a week; 140-fold dose reduction	Drug concentrations over 30 ng/mL for 15 days
(Cousins et al., 2011)	KT	1	ATZ/r	1.5mg twice daily TAC resulted in high concentrations	Drug concentrations as high as 160 ng/mL were reported
(Akhtar et al., 2011)	SPK	1	DRV/r; ETV; RAL	1mg every week	C_{trough} concentrations 8 to 15 ng/ml
(van Maarseveen and van Zuilen, 2013)	KT	4	LPV/r; DRV/r; +/-ETV, EFV, NVP	2, 1.5, 2, and 2 mg loading dose (0.01 to 0.1mg/kg)	Median C_{trough} concentrations 17.8 ng/mL; pre-KT CNI trial 12h AUC showed no peaks

Key: KT, kidney transplant; OLT, orthotopic liver transplant; SLK, simultaneous liver-kidney transplantation; SPK, simultaneous kidney–pancreas transplantation; q, every; h, hours; CsA, cicloposrin; Tac, tacrolimus; ATZ, atazanavir; DRV, darunavir; EFV, Efavirenz; ETV, etravirine; LPV, lopinavir; NVP, Nevirapine; NFV, nelfinavir; SQV, saquinavir; /r, ritonavir boosted

Table 29: **Summary of Evidence (case studies, case series, prospective studies) of CNI and Drug Interactions with PI-Containing Antiretroviral Drug Therapy**

PI Sparing ART					
Publication	**Organ**	**N**	**ART Regimen**	**Effect on Dose administered**	**Effect on whole blood concentrations**
Ciclosporin					
(Frassetto et al., 2007)	KT & OLT	35 (20 KT, 15 OLT)	EFV, NVP	EFV – ~50% dose increments NVP - Minimal dose adjustments	30% lower C_{trough} concentrations reported with EFV despite dose adjustments. The trough/dose ratio for EFV is less than half that of NVP.
(Gruber et al., 2008a)	KT	8	NVP	50 to 150mg q 12h vs 175 to 200mg q 12h in NRTI only cART	C_{trough} concentrations not reported; doses aimed at achieving C_{trough} concentrations of 225 to 300 ng/ml.
(Tricot et al., 2009b)	KT & OLT	13	RAL	KT: 10 mg q 24h OLT: 175 to 250 mg q 24h	KT: C_2 400 ng/ml OLT: $C_0$135 to 218 ng/ml
Tacrolimus					
(Tan et al., 2004a)	KT	3	Not specified	16mg every other day	3.0ng/ml C_{trough} concentrations
(Frassetto et al., 2007)	KT & OLT	35 (20 KT, 15 OLT)	EFV, NVP	3.1 ± 1.4mg every 12h vs 7 to 9mg every 12h in ARV naïve patients.	C_{trough} concentrations achieved 6.4 ± 2.9ng/ml vs 3 to 30ng/ml in ARV naïve patients.
(Tricot et al., 2009b)	KT & OLT	13	RAL	KT: 7 to 24 mg q 24h OLT: 0.5 to 10 mg q 24h	C_{trough} concentrations:- KT: 7.1 to 10.5 ng/ml OLT: 3.4 to 9.2 ng/ml
(Miro et al., 2010)	SPK	1	RAL	1.8 to 4.1 mg q 24h	C_{trough} concentrations 5.7 to 19.2 ng/ml

Key: KT, kidney transplant; OLT, orthotopic liver transplant; CsA, cicloposrin; EFV, Efavirenz; h, hour; NVP, Nevirapine; NRTI, nucleoside/tide reverse transcriptase inhibitor; SQV, saquinavir; cART, combination antiretroviral drug therapy; $C_{0,}$ C_{trough} concentrations.

Purpose of study

The main aim of this study was to describe the calcineurin whole blood concentrations attained in clinical practice for HIV positive kidney transplant recipients in the first year post-transplantation. In particular, to determine the extent target range CNI whole blood concentrations were achieved and maintained during the first 12 month post-HIV/KT.

Primary aims

Aim 1: To describe CNI trough whole blood concentrations achieved and associated doses during the first 12 months post-transplant.

Aim 1A: To describe the time and dose to achieve the first therapeutic trough whole blood concentration during the first 14 days post-transplant.

Aim 1B: To describe the proportion of therapeutic trough whole blood concentrations achieved and associated doses in the 'early' (0 to 12 weeks) phase post-transplant.

Aim 1C: To describe maintenance trough whole blood concentrations and associated doses in the 'late' (6 to 12 months) phase post-transplant.

5.2. Method

Patient Enrolment

For this chapter, data were used for all enrolled HIV+ study subjects. Enrolled patients were stratified into two groups, those on ciclosporin (CsA) and tacrolimus (Tac) based CNI therapy at the point of transplantation. All patients were included in chapter analyses unless they met any exclusion criteria.

Exclusion criteria

1. Patients that took other non-calcineurin inhibitor based therapy at transplantation for example, mammalian target of rapamycin (mTOR) inhibitors (e.g sirolimus).
2. Post-dose CNI concentrations were excluded.
3. Patients with incomplete data on CNI dosing and C_{trough} drug concentrations (fewer than 3 drug concentration measurements).
4. Patients that received non-oral CNI formulations (e.g. intravenous infusions).
5. Patients that did not start CNI therapy immediately post-transplantation.
6. Patients that had an ABO incompatible transplant and those that received alemtuzumab for induction therapy.

CNI Drug Concentration Analyses

Calcineurin inhibitor whole blood concentrations were all assumed to represent trough values, defined as the concentration prior to the next dose, irrespective of dosing interval i.e. 12 or 24 hourly. Any CNI concentrations not taken pre-dose, e.g. in the case of extended interval dosing regimens, were excluded from the analyses. Data were analysed for specific time points post -transplant i.e. 1, 2, 4, 6, 8, 12, 24, 36 and 52 weeks post-KT. Patients were censored at date of clinic event (allograft rejection), date CNI drug is discontinued or switched or, date of last clinic visit up to 1 year post-KT. Whole blood concentrations were included for analysis where they fell within 14 days of the specific time point and steady state conditions were likely (Oo et al., 2008).

Target C_{trough} CNI drug concentrations for the first year post-transplantation varied between centres and also over the study period where practices changed. Target ranges were also guided by clinic events e.g. acute rejection or suspected CNI toxicity. There was also variability in target ranges throughout the first year post-transplant with consideration for high immunological risk group of patients. For these reasons, analyses was standardised as follows

- Ciclosporin C_{trough} target range: 200-350 ng/mL during weeks 1-12, 100 – 250 ng/mL thereafter;
- Tacrolimus C_{trough} target range: 8-15 ng/mL during weeks 1-12, 5-10 ng/mL thereafter.

Initiating doses were as per local protocol except when the pre-transplant CNI trial dosing strategy (Bhagani et al., 2006) was utilised. Total daily CNI doses were calculated by multiplying the single dose by dose frequency [units expressed as mg/day]; for weight adjusted doses this was calculated by dividing the CNI dose by the weight in kilograms [units expressed as mg/kg]; and dose adjusted C_{trough} concentrations were calculated by dividing the drug concentration by the dose [units expressed as ng/ml per mg or mg/kg for weight adjusted doses].

Assumptions

All CNI drug concentrations reported were assumed to be true trough values, assayed using validated approaches. All patients were assumed to be 100% adherent with their medicines.

Statistical analysis

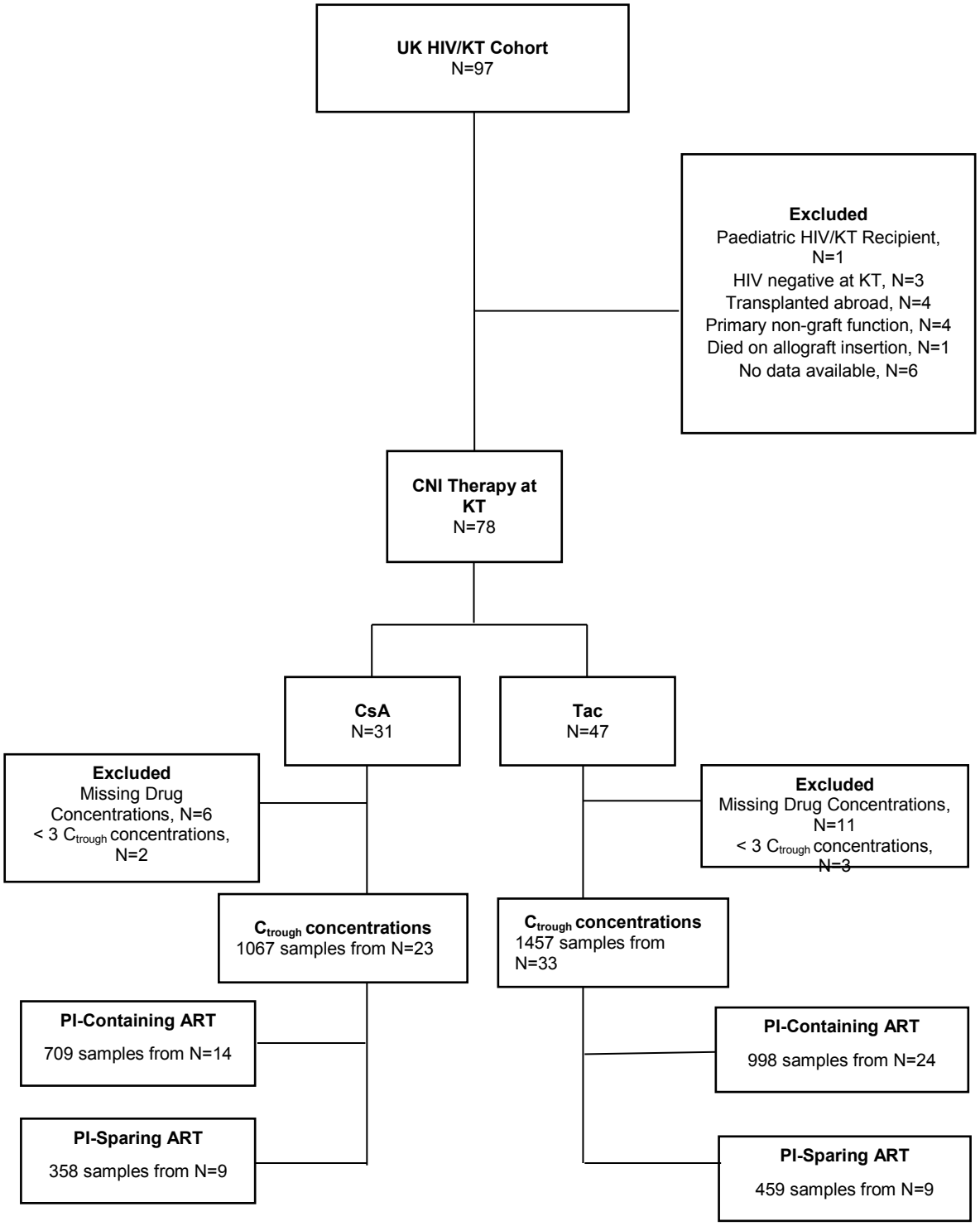
Descriptive statistical tests were used for analyses in this chapter. Univariate analyses of baseline recipient characteristics stratified *a priori* by CNI choice at transplantation i.e. ciclosporin vs tacrolimus were tested for statistical significance using Fisher's exact test (2-sided) where values were < 5 and chi-squared test (2-sided) where values were >5 (considered statistically significant if $p < 0.05$); Wilcoxon rank-sum for medians or T-tests for means. Z-tests were used to compare proportions.

5.3. Results

Patient Disposition

There were 97 HIV Kidney Transplant (KT) recipients identified that were transplanted up to 31st December 2013. Those that did not meet the study inclusion criteria (N=19) included: one patient less than 18 years of age; four transplanted abroad (India, Belgium, Berlin and USA); three that acquired HIV post-transplantation; one patient who died during KT, four with primary non-graft function and six that had no data. The six patients were transplanted at Oxford Radcliffe hospital (n=4), Birmingham (n=1) and Manchester (n=1). All were referrals from external HIV centres (unknown) and received post-transplant follow-up at their base hospitals. Of the remaining 78 patients, 31 patients were taking ciclosporin and 47 tacrolimus based IS therapy. In the CsA group, the excluded patients included 6 patients without any drug concentrations reported and 2 patients with < 3 available drug concentrations. Of the 8 patients that were excluded, 5 were transplanted at GSTT, one at St Barts Hospital and two at the Royal Free hospital. The reasons for missing drug concentrations were as follows: switching therapy to Tac in the early period post-transplant (n=5) and loss to follow-up (n=3). In the Tac group, there were 11 patients with no drug concentration values reported and 3 with < 3 drug concentrations available. Of the 14 patients excluded from the analyses the participating centres were St Helier hospital (n=1), Luton & Dunstable hospital (n=1), Edinburgh (n=1), Manchester (n=6), Birmingham (n=1) and Imperial (n=3). The reasons for missing drug concentrations were as follows: lost medical notes; implementation of new electronic medical records; lost to follow-up; inaccessibility due to geographical location (Glasgow & Edinburgh); and unable to access follow-up data from the referring base hospitals.

Figure 27: Patient disposition for UK HIV/KT cases stratified by those on Ciclosporin and Tacrolimus based Immunosuppression Therapy



Patient Characteristics

56 patients met the inclusion criteria and allowed in-depth analysis of their CNI drug concentrations (see **Figure 27**). Twenty three of these received ciclosporin and 33 tacrolimus based IS therapy. The ciclosporin (CsA) and tacrolimus (Tac) groups were well matched for baseline characteristics except for antiretroviral drug choice at KT where a higher proportion of PI-containing ART regimen was used in the CsA group compared to the Tac group ($p<0.05$). Patients in the CsA group were more likely to have taken part in a pre-KT CNI dosing trial ($p<0.01$), refer to **Table 30** and **Table 31**. The median (IQR) age at KT of the recipients was 44 (38, 50) years with a slightly younger cohort constituting the CsA group 39 (37, 49) vs 46 (40, 51) years.

The 56 patients yielded a total of 2524 whole blood drug concentrations for analyses; 42% (1067 samples) in the CsA group and 58% (1457) in the Tac group. The median (IQR) number of samples per patient were 43 (39, 58) for the CsA group 36 (29, 43) for the Tac group.

Table 30: Baseline patient characteristics at kidney transplantation according to CNI immunosuppression therapy

n (%)		Ciclosporin N = 23	Tacrolimus N = 33	P value*
Age, median(IQR)	Years	39 (37, 49)	46 (40, 51)	0.06
Gender, n (%)	Male	18 (78)	20 (60)	0.16
Ethnicity, n (%)	Black	17 (74)	27 (82)	0.48
Cause of ESKD, n (%)	HIVAN	14 (61)	16 (48)	0.54
Duration of pRRT, median(IQR) ǂ	Years	4 (2, 6)	7 (4, 7)	0.07
HIV parameters, median(IQR)				
CD4 count at KT	Cells/mm^3	377 (271, 566)	350 (273, 504)	0.66
Co-morbidities, n (%)				
Diabetes		4 (17)	4 (12)	0.58
Hypertension		22 (96)	31 (94)	0.78
Hepatitis B co-infection, n (%)		5 (22)	4 (12)	0.34
Hepatitis C co-infection, n (%)**		3 (13)	1 (3)	0.17
Graft characteristics				
Allograft type, n (%)	Cadaveric	12 (52)	24 (73)	0.11
HLA mismatch, median(IQR) ŧ		3 (1, 4)	3 (2, 4)	0.41
Donor/Recipient CMV mismatch status, n (%)	D+/R-	1 (4)	1 (3)	0.79
Antiretroviral drug therapy (ART) choice, n (%)				
PI-containing ART		14 (61)	9 (27)	0.01

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test; comparing proportions (%), chi-squared test (2-sided). Statistically significant ($p < 0.05$); Missing values - **n=2, ǂ n=6, ŧn=7.

Table 31: Immunosuppression drug therapy management in the first year post-transplant

	Ciclosporin N=23 (%)	Tacrolimus N=33 (%)	P value
Induction therapy[b]			
AntiCD25 monoclonal antibody	21 (91)	32 (97)	0.35
Other	2 (9)	1 (3)	
Triple IS regimen[a]	23 (100)	33 (100)	NS
CNI treatment crossover	16 (50)	1 (3)	0.36
Ciclosporin	-	-	
Tacrolimus	9 (39)	-	
Sirolimus	1 (4)	-	
Reason for CNI crossover			
Acute rejection	7	-	
CNI toxicity	1	-	
Other	2	-	
Pre-transplant CNI dose finding trial	13 (57)	4 (12)	**0.00**

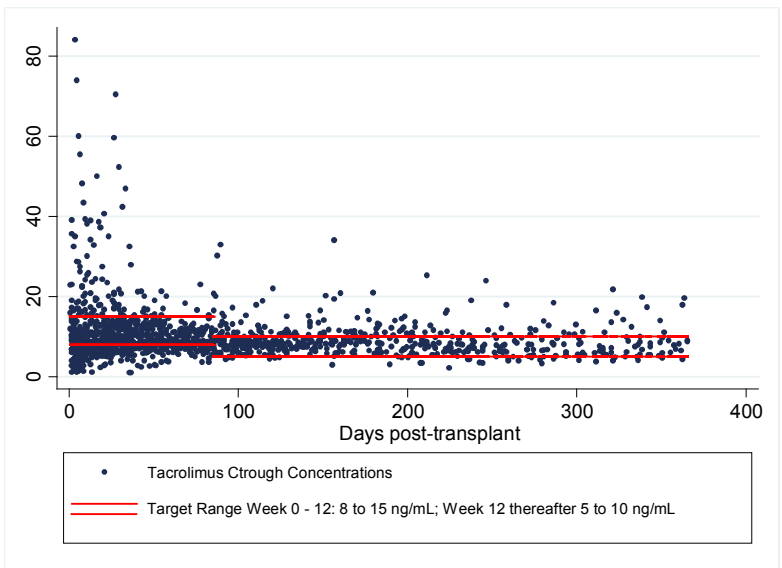
Key: IS – immunosuppression, CNI – calcineurin inhibitor; [a]Calcineurin inhibitor + Mycophenolate or Azathioprine + corticosteroids; Comparing proportions (%), chi-squared test (2-sided); statistically significant ($p < 0.05$).

Overall distribution of CNI C_{trough} drug concentrations

The overall distribution of C_{trough} concentrations throughout the first year post-transplantation of the UK HIV kidney transplant recipients (n=56) are shown in **Figure 28** and **Figure 29** for tacrolimus and ciclosporin patients respectively. In the CsA group, majority of the C_{trough} drug concentrations were within the target range were 52% at weeks 0 to 12 and 79% at months 6 to 12. However, in the Tac group there were lower target concentrations observed in the early period post-KT, week 0 to 12 (44%), compared to the late period post-KT, month 6 to 12 (64%). The proportions of C_{trough} concentrations in the early period post-KT was significantly different when CsA was compared to Tac, (respectively 52% vs 44%, p=0.002). Likewise, in the late period post-KT the proportion of target C_{trough} concentrations were significantly higher in the CsA compared to Tac, (respectively 79% vs 64%, p=0.0000). C_{trough} drug concentrations for both groups were positively skewed (not normally distributed) with an overall mean of 218 (163, 282) ng/ml and 8 (6, 10) ng/ml for Tac and CsA groups respectively.

Figure 28: Overall Distribution of Tacrolimus C_{trough} Concentrations in the First Year Post-HIV/KT

A. Scatter plot of all Tac C_{trough} concentrations available



B. Histogram of all Tac C_{trough} concentrations available

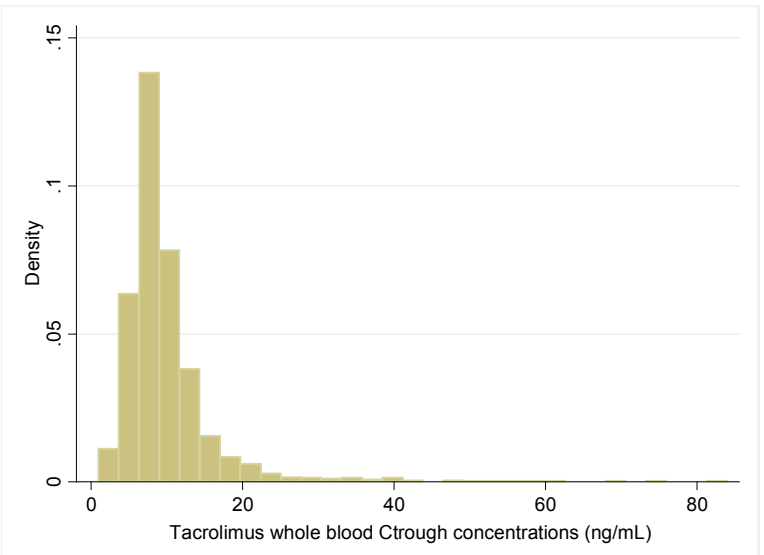
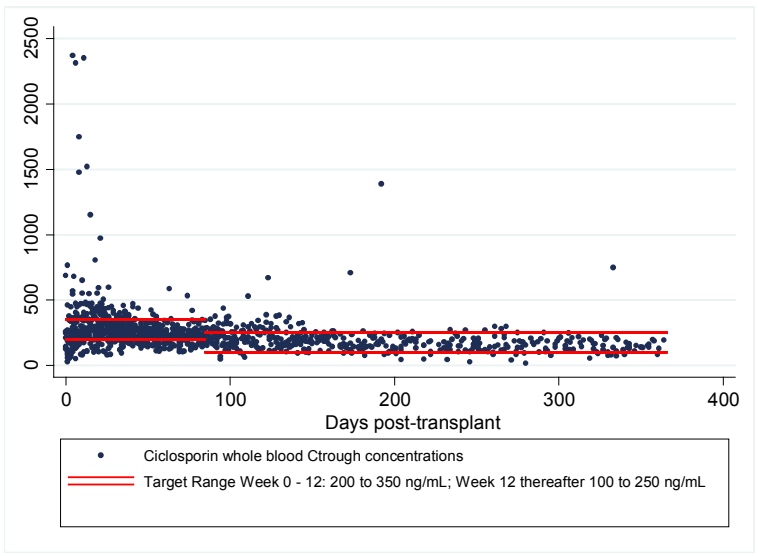
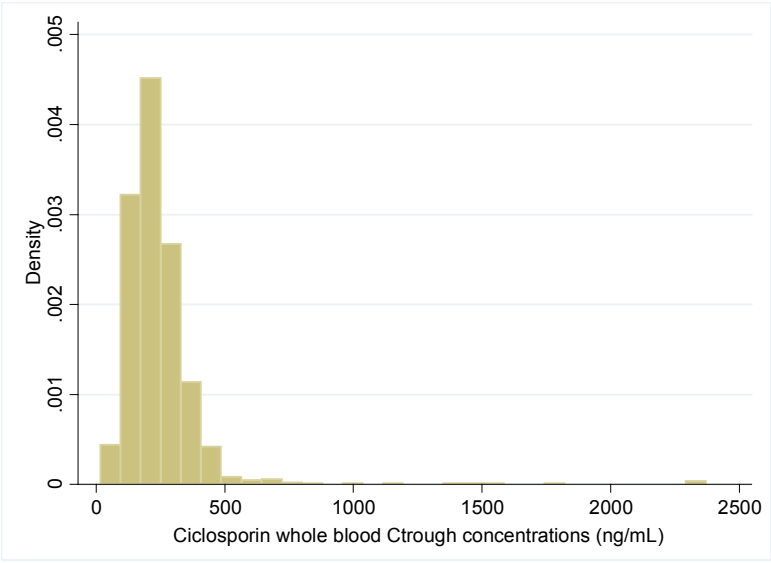


Figure 29: Overall Distribution of Ciclosporin C_{trough} Concentrations in the First Year Post-HIV/KT

A. Scatter plot of all CsA C_{trough} concentrations available



B. Histogram of all CsA C_{trough} concentrations available



Overall, there were similarities in the time to achieve therapeutic C_{trough} drug concentrations between CNI groups, median (IQR) were 3 days (1, 20) for Tac and 4 days (2, 12) for CsA post-KT. Throughout the follow-up period, fluctuations in the C_{trough} concentrations were observed in both CNI groups; however, this seemed to stabilise in the late period (6 to 12 months) post-transplant (see **Figure 28**). By week 4 post-transplant, more than half of the patients in both CNI groups had achieved therapeutic concentrations i.e. 50% Tac (n=33) vs 57% for CsA (n=23). Analyses stratified by cART choice observed significant differences in C_{trough} drug concentrations for both CsA and Tac groups in the early period post-transplant. The mean ± SD Tac C_{trough} concentrations at week 1 post-KT for those taking PI-containing vs PI-sparing cART were significantly different, respectively 19.2±13.0 vs. 6.3±2.9, p=0.002 (see **Figure 28B** and **Table 32**). Thereafter, the mean C_{trough} concentrations post-KT were similar. There were similar findings in the CsA group where week 1 post-KT C_{trough} concentrations were significantly higher in those taking PI-containing cART compared to PI-sparing cART respectively, 496±610 vs 184±96, p=0.01. From week 2 post-KT onwards, there were no statistical differences between the cART groups, (see **Figure 28D**).

CNI Doses required to Achieve Therapeutic C_{trough} Concentrations

When considering CNI doses used to achieve therapeutic C_{trough} concentrations, in the CsA group those on PI-containing cART dosing required a 10 fold dose reduction on average 1mg/kg/day (standard dose 10 to 15mg/kg/day (NovartisLtd, 2014)) which remained consistent throughout the 12 months of follow-up (see **Figure 28A**). By contrast, CsA doses in the PI-sparing regimen group were similar to standard doses although, required progressive dose reductions with lower maintenance doses used in the later months post-KT (see **Figure 28B**). This was in line with local protocols to minimise CNI exposure.

In those taking tacrolimus, a profound dose reduction approximately 100 fold (standard dosing 0.10-0.20 mg/kg/day (SandozLtd, 2013)) was required when co-administered with PI-containing cART (see **Table 32** and **Figure 28C**). There were very few dosing alterations made throughout the study period. However, in the PI-sparing group somewhat higher Tac doses were used compared to standard dosing in the early period post-KT (see **Figure 28D**). For the remaining follow-up period doses were maintained at <0.2mg/kg/day. Ethnicity did not impact the CNI doses and whole blood concentrations achieved when stratified a priori by cART choice (see **Table 32A** and **Table 32B**) although; the patients numbers in the sub-groups were low.

Table 32: **Mean (±SD) calcineurin doses & Mean (±SD) whole blood concentrations in HIV positive kidney transplant recipients**

Weeks Post-KT	Ciclosporin					Tacrolimus				
	All patients N=23	PI-containing cART N=14		PI-sparing cART N=9		All patients N=33	PI-containing cART N=9		PI-sparing cART N=24	
	C_t (ng/ml) [b]	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml) [c]	C_t (ng/ml)	Dose (mg/kg/day)	C_t (ng/ml)	Dose (mg/kg/day)
1	375±497	496±610	1.3±1.7	184±96	9.6±4.5	9.8±9.1	19.2±13.0[a]	0.0194±0.0225	6.3±2.9[a]	0.13±0.09
2	333±291	402±361	0.8±0.6	233±88	11.0±4.3	10.0±5.9	15.1±8.4[a]	0.0025±0.0017	8.2±3.3[a]	0.18±0.11
4	245±93	237±76	0.7±0.5	259±119	10.6±4.5	12.3±11.2	19.5±21.3[a]	0.0024±0.0034	10.0±3.6[a]	0.24±0.11
6	253±89	255±86	0.5±0.2	250±99	10.2±4.5	10.6±5.6	12.4±9.4[a]	0.0013±0.0006	10.0±3.5[a]	0.24±0.12
8	236±69	224±75	0.4±0.1	260±53	11.6±4.1	9.2±3.2	8.7±4.1	0.0013±0.0010	9.4±2.9	0.22±0.11
12	231±61	238±53	0.4±0.2	217±53	10.7±4.4	9.4±3.6	10.8±5.2	0.0016±0.0020	8.9±2.8	0.20±0.11
24	180±45	186±30	0.4±0.2	171±64	6.6±2.5	9.7±4.1	8.9±4.4	0.0014±0.0013	10.0±4.0	0.18±0.09
36	165±41	167±46	0.4±0.2	163±36	6.5±2.0	8.1±3.3	8.1±4.0	0.0015±0.0013	8.1±3.1	0.18±0.09
52	129±36	142±42	0.4±0.2	119±32	6.4±2.0	9.2±4.4	7.0±1.6	0.0015±0.0015	9.9±4.8	0.14±0.10

Comparing means t-test, statistically significant P<0.05. [a] P <0.05 (PI-containing cART vs. PI-sparing cART); [b] Target range: 200-350 ng/mL during weeks 1-12, 100 – 250 ng/mL thereafter; [c] Target range: 8-15 ng/mL during weeks 1-12, 5-10 ng/mL thereafter.

Table 32A: **Mean (±SD) Ciclosporin doses & Mean (±SD) whole blood concentrations in HIV positive kidney transplant recipients stratified by Ethnicity**

Weeks Post-KT	All patients N=23	PI-containing cART				PI-sparing cART			
		Black Ethnicity N=11		Other Ethnicity N=3		Black Ethnicity N=6		Other Ethnicity N=3	
	C_t (ng/ml) [b]	C_t (ng/ml)[b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)
1	375±497	543±670	1.4±1.9	285±122	0.7±0.08	176±39	11.6±3.3[a]	205±221	4.6±2.4[a]
2	333±291	315±144	0.8±0.6	695±721	0.8±0.1	235±111	12.8±2.7	229±23	7.5±5.4
4	245±93	238±85	0.7±0.6	232±38	0.5±0.2	305±114	12.4±3.2	167±73	7.1±5.2
6	253±89	266±91	0.5±0.2	218±66	0.4±0.2	252±100	11.8±3.6	245±118	7.1±5.2
8	236±69	232±76	0.4±0.1	192±76	0.4±0.2	240±48	12.8±3.2	312±21	8.7±6.0
12	231±61	223±63	0.4±0.2	285±58	0.5±0.1	232±52	12.3±3.6	188±57	7.5±5.3
24	180±45	184±32	0.4±0.2	200[c]	0.37[c]	190±42	8.4±0.6	153±86	4.8±2.6
36	165±41	167±46	0.4±0.2	-[d]	-[d]	161±33	4.9±2.9	166±54	7.5±0.4
52	129±36	142±42	0.4±0.2	-[d]	-[d]	135±22	7.5±0.4	96±36	4.9±2.9

Comparing means t-test, statistically significant P<0.05. [a] P <0.05 (Black vs. Other; [b] Target range: 200-350 ng/mL during weeks 1-12, 100 – 250 ng/mL thereafter; [c]Data available n=1; [d]Data available n=0.

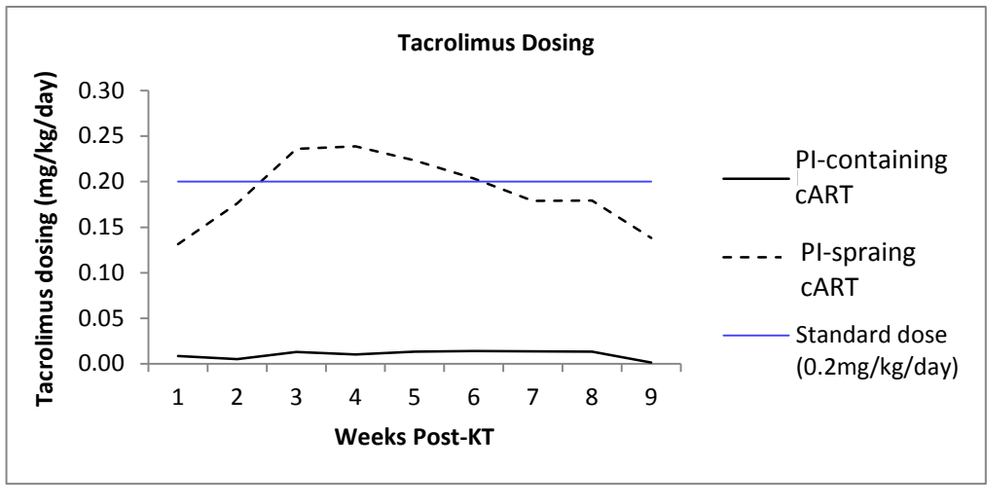
Table 32B: **Mean (±SD) Tacrolimus doses & Mean (±SD) whole blood concentrations in HIV positive kidney transplant recipients stratified by Ethnicity**

Weeks Post-KT	All patients N=33	PI-containing cART				PI-sparing cART			
		Black Ethnicity N=8		Other Ethnicity N=3		Black Ethnicity N=19		Other Ethnicity N=3	
	C_t (ng/ml) [c]	C_t (ng/ml)[b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)	C_t (ng/ml) [b]	Dose (mg/kg/day)
1	9.8±9.1	21.2±14.6	0.02±0.02	12.9±4.6	0.009±0.008	6.2±2.9	0.17±0.07	5.8±2.7	0.12±0.06
2	10.0±5.9	16.7±9.1	0.003±0.002	10.7±4.6	0.002[c]	8.0±3.4	0.21±0.10	8.2±4.0	0.15±0.03
4	12.3±11.2	24±23	0.003±0.004	6.1±0.07	0.001±0.0001	9.8±3.4	0.25±0.12	11.6±4.9	0.17±0.04
6	10.6±5.6	12.9±10.4	0.001±0.001	10.6±6.8	0.002±0.0004	10.1±3.5	0.25±0.12	11.0±2.5	0.17±0.04
8	9.2±3.2	9.2±4.0	0.001±0.001	7.0±5.6	0.001±0.0001	9.5±3.01	0.25±0.11	9±2.8	0.17±0.04
12	9.4±3.6	11.2±5.8	0.002±0.002	9.5±3.5	0.001±0.001	8.9±2.8	0.22±0.10	8.3±3.	0.16±0.06
24	9.7±4.1	9.5±4.8	0.001±0.001	7.0±1.5	0.001±0.001	9.7±3.7	0.20±0.07	12.1±5.4	0.15±0.05
36	8.1±3.3	8.7±3.8	0.001±0.002	6.3±5.7	0.002±0.0003	7.5±2.3	0.20±0.08	11.6±5.09	0.17±0.03
52	9.2±4.4	6.5±1.4	0.001±0.002	9.1[c]	0.002[c]	8.9±4.1[a]	0.19±0.07	15.5±5.8[a]	0.17±0.03

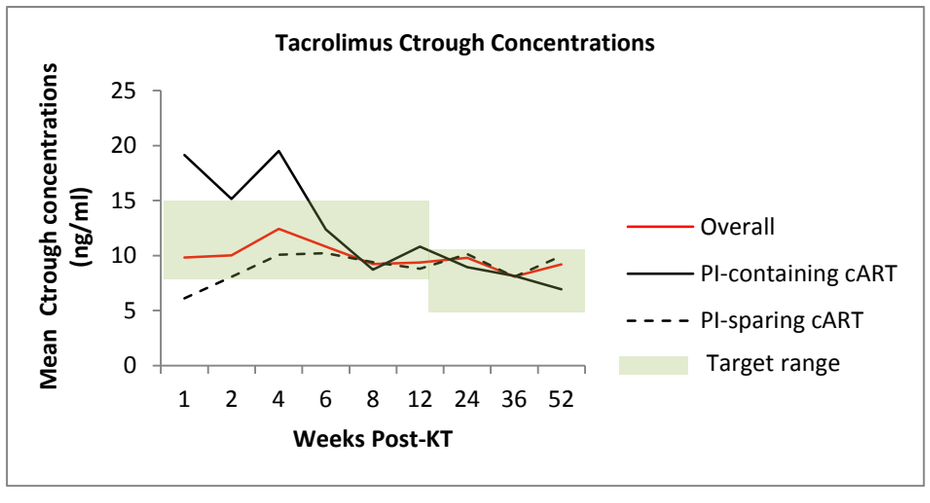
Comparing means t-test, statistically significant P<0.05. [a] P <0.05 (Black vs. Other; [b]Target range: 8-15 ng/mL during weeks 1-12, 5-10 ng/mL thereafter; [c]Data available n=1.

Figure 30: Tacrolimus and Ciclosporin Dosing and C_{trough} Concentrations Stratified by cART Choice

A

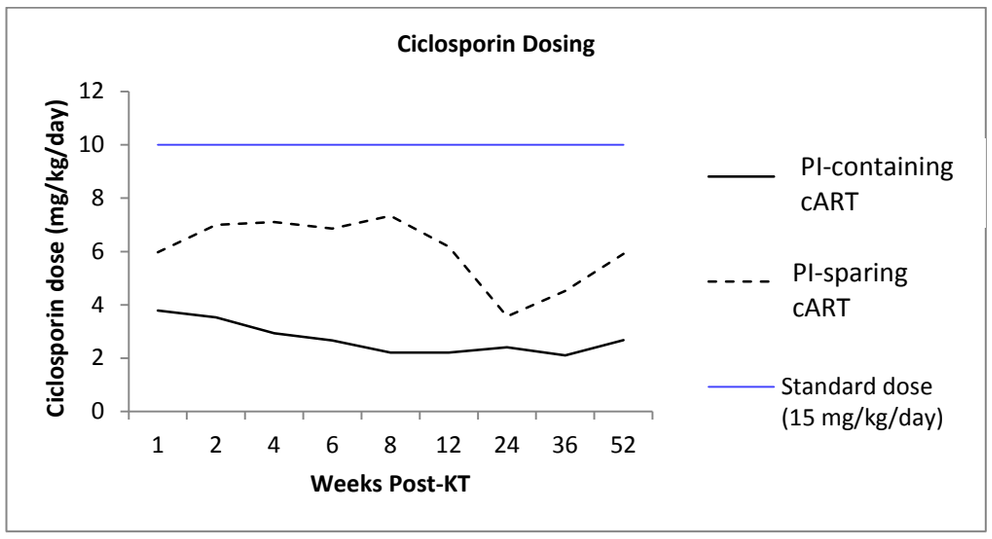


B

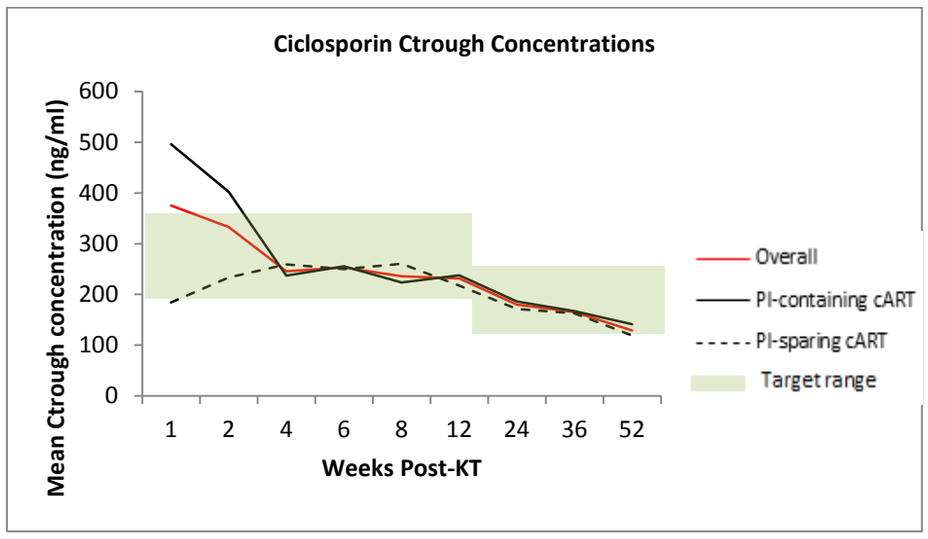


	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 24	Week 36	Week 52
P-value	0.002	0.08	0.96	0.77	0.70	0.57	0.21	0.64	0.12

C



D

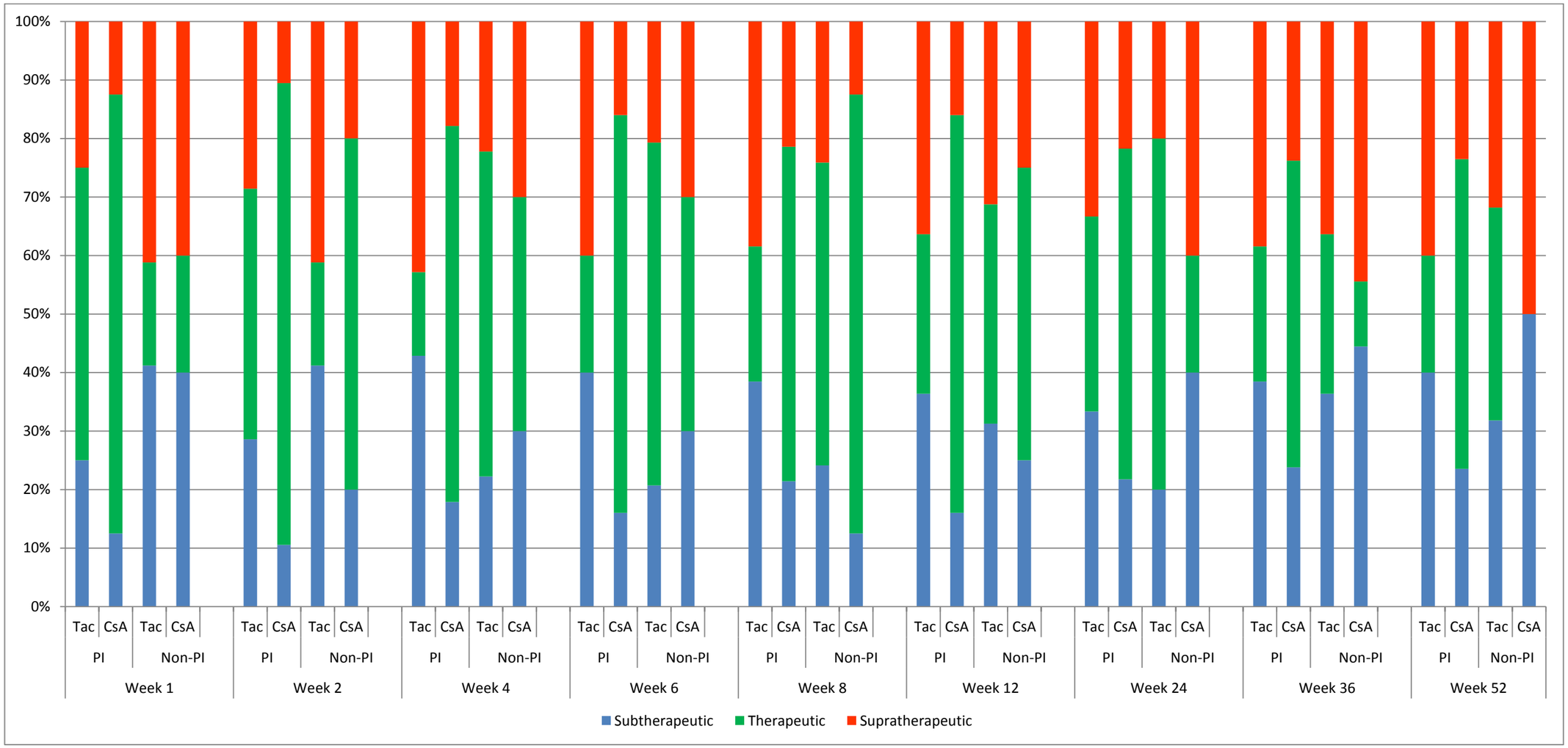


	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 24	Week 36	Week 52
P-value	0.01	0.13	0.90	0.71	0.23	0.43	0.64	0.68	0.33

Graph showing CNI dosing and mean C_{trough} concentrations over the first year post-KT stratified by cART choice. A comparison to standardised CNI dosing is depicted in the graph. (A) Tacrolimus dosing (B) Tacrolimus C_{trough} concentrations (C) Ciclosporin dosing (D) Ciclosporin C_{trough} concentrations. P-values included in the tables were calculated using Wilcoxon-ranksum test comparing PI-containing vs PI-sparing (Non-PI) for each time point post-transplant.

Further analyses of the proportions of CNI C_{trough} concentrations, found that irrespective of CNI choice one third of patients observed sub-therapeutic CNI C_{trough} concentrations throughout the first 12 weeks post-KT (see **Figure 31**). When comparing proportions of supratherapeutic vs subtherapeutic C_{trough} concentrations achieved, there were significant differences between PI-containing and PI-sparing cART respectively, 19% vs 41%, p=0.01 at week 1 and 12% vs 42%, p=0.0005 at week 2 and 18% vs 39%, p=0.002 at weeks 6, 8, 12 for those taking Tac. There were no significant differences found at weeks 4, 24, 36 and 52. In the CsA group, significant differences PI-containing and PI-sparing cART were observed at weeks 1 (17% vs 39%, p=0.005), week 2 (26% vs 9%, p=0.004), week 24 (22% vs 4%, p=0.000) and week 52 (43% vs 4%, p=0.000) respectively. Comparisons made at weeks 4, 6, 8, 12, and 36 were not statistically significant.

Figure 31: Trough drug concentrations (C_{trough}) in the first year following KT in HIV positive patients



Proportion of patients with whole blood concentrations above, within, and below the target range. Ciclosporin target range: 200-350 ng/mL during weeks 1-12, 100 – 250 ng/mL thereafter; Tacrolimus target range: 8-15 ng/mL during weeks 1-12, 5-10 ng/mL thereafter. Patients are stratified by CNI and ART choice at KT. Follow up was censored at CNI switch.

5.4. Discussion

Post-transplant management of HIV infected kidney transplant recipients is complicated by the significant drug interactions between calcineurin inhibitors and antiretroviral drugs. There are clinical pharmacokinetic studies reported in the literature for various CNI and cART combinations albeit with limited information reported on achieving and maintaining CNI drug concentrations in clinical practice. Analyses in this chapter have demonstrated (1) the challenges of achieving protocol guided target concentrations especially in those taking PI-containing cART regimens. Supratherapeutic concentrations were frequent in the PI-containing cART group particularly in the first four weeks post-KT where concentrations were up to 3 times higher compared to the PI-sparing group. (2) significant dose adjustments were required to achieve target CNI concentrations for those on PI-containing cART; dose reductions up to 100 fold for Tac and 10 fold for CsA. Minimal dose adjustments were required for those taking PI-sparing cART. (3) challenges in maintaining target concentrations with frequent sub-therapeutic concentrations throughout the follow-up period mostly for those taking PI-sparing cART. In the first 3 months post-KT, almost one third of CNI concentrations were sub-therapeutic. (4) Ethnicity did not impact the CNI doses and whole blood concentrations achieved when stratified a priori by cART choice although; the patient numbers in the sub-groups were low.

Early period post-KT

At KT, both CNI groups were well matched with the exception of cART choice where those in the ciclosporin group had a higher proportion of those taking PI-containing cART compared to those taking tacrolimus (61% vs 27%, p=0.01). This is not surprising as dosing of CsA with PI-containing drugs required approximately 10 fold dose reduction which allowed for a less complicated and shorter dosing interval (24h vs 168h) compared to Tac that required ~100 fold dose reduction.

Dosing of CNIs in this early period can be complicated by multiple factors apart from drug interactions. Briefly, the haemodynamic changes post-KT (Williams and Lake, 1992, Kostopanagiotou et al., 1999), use of gastric acid suppressants that alter gut pH (Lemahieu et al., 2005b), corticosteroid withdrawal (Anglicheau et al., 2003), pharmacogenomics (Macphee et al., 2002, MacPhee, 2012), gut motility (Hochleitner et al., 2001, Lemahieu et al., 2005b) or use of antibiotics that may affect gut flora (Lee et al., 2015) are all factors that could influence CNI exposure during this early period post-KT. When managing drug interactions, the time it takes for metabolic enzyme or transporter inhibition/induction should also be considered (Reitman et al., 2011). However, in our patient cohort it was recommended that recipients be stable on cART for at least 6 months prior to transplantation (Bhagani et al., 2006). Therefore, pre-emptive DDI management was essential as it was assumed that the metabolic/transporter inhibition/induction processes were well established by transplantation.

Both CNI groups observed a large interpatient variability in the distribution of CNI C_{trough} concentrations over the first 12 weeks post-KT. This meant multiple alterations in CNI dosing to achieve target CNI C_{trough} concentrations. For both CNI groups taking PI-sparing cART, therapeutic doses used were comparable to those used in the general population (CsA ~10 vs 10-15 and Tac ~0.2 vs 0.1-0.2 mg/kg/day respectively). Similar interpatient variations have been observed in the general population for both CNI drugs. In the Symphony study (Ekberg et al., 2009b), a large multicentre clinical trial on immunosuppressive regimens, reported approximately 50% of patients (n=1589) achieved CNI concentrations within target range (Tac 3-7 ng/mL; CsA 50-100 ng/mL) over the first year post-KT. An evaluation of the CNI C_{trough} concentrations achieved in the first week post-KT, in our cohort ~43% (58% CsA vs 30% Tac) of patients achieved target concentrations compared to the Symphony study that reported between 43% for low dose CsA (2 - 4mg/kg/day) and 51% or low dose Tac (0.1mg/kg/day). There are a few possible explanations for this first; clinicians may have taken a more cautious approach particularly when dosing Tac that required extended dosing interval when co-administered with PI-containing cART. Secondly, there was a significantly higher proportion of patients taking PI-containing cART (P-gp/CYP inhibitors) in the CsA group compared to the Tac group allowing for target steady state C_{trough} concentrations to be achieved much quicker. Finally, evidence suggests a strong relationship between Tac bioavailability and intestinal abnormalities while CsA bioavailability remains unaffected (Maes et al., 2002).

By week 2 in our study, those that achieved target CNI C_{trough} concentrations showed more stability over subsequent weeks. Similar to the Symphony study, those that achieved supratherapeutic CNI C_{trough} concentrations by week 2 took longer to achieve target concentrations (up to 8 weeks in both groups). Although it is noteworthy, the Symphony study used much lower CNI doses and much lower target concentrations as KT recipients were considered at low risk of rejection unlike our cohort who considered high risk (Stock et al., 2010a, Locke et al., 2014).

Late period post-KT

In the late period post-transplant, months 6 to 12, CNI drug concentrations are expected to have stabilised and achieved steady state. Often in this period, clinicians make dose reductions to minimise CNI exposure to avoid nephrotoxicity (Schiff et al., 2007). The local protocols used for the current analyses followed a similar approach, Tac target concentrations reduced to 5 - 10 ng/mL and CsA to 100 – 250 ng/mL for months 6 to 12 post-KT. Throughout the follow-up period, up to one third of the overall Tac concentrations were subtherapeutic compared to one fifth of CsA concentrations. High intrapatient variability in the later period post-KT can adversely impact the allograft (Borra et al., 2010b, Stevenson et al., 2011). Borra et al (2010) performed analyses of Tac drug concentrations drawn from months 6 to 12 in an outpatient setting. The authors found in multivariable analyses that within patient variability of Tac clearance was strongly associated with allograft failure (high intrapatient variability with no graft failure (n=263) 47.5% vs those with graft failure (n=34) 70.6%, p=0.003). In another study, high intrapatient variability throughout the first year post-KT resulted in a higher allograft rejection rate compared to those with low intrapatient variability (19.4% vs 8.2% respectively, p=0.02). In the

current dataset, it was challenging to ascertain the impact of allograft rejection due to the sample size when stratified into three sub-groups (CNI choice, cART regimen and allograft rejection). However, in Chapter 4 more than half of allograft rejection episodes occurred in the first 14 days post-KT in the Tac group (AR rate at 1 year 21%) compared to CsA that occurred in the over the first 9 months post-KT (AR at 1 year 58%). It was therefore probable that the variability of the drug concentrations may have been skewed by the differences between CNI groups in AR rates and the timing of AR.

Nevertheless, the analysis of CNI C_{trough} concentrations only provides partial information on drug exposure. For example, the extended dosing interval with Tac and PI-containing cART has demonstrated a significant change in the total drug exposure (AUC) of Tac. A pharmacokinetic study performed in 8 HIV+ transplant patients on PI-containing cART observed an AUC that was almost 12 times greater than AUC of non-HIV transplant recipients (median [IQR] respectively, 24996 [18205–41601] vs 2000–5000 ng*hr/mL/mg/kg at weeks 2 to 12 post-KT). By contrast, CsA AUC was lower in HIV+ transplant recipients (n=34) (median [IQR] respectively, 5759 [3325–8045] vs 7000–9000 ng*hr/mL/mg/kg at weeks 2 to 12 post-KT) (Frassetto et al., 2013). In some instances ritonavir has altered Tac AUC from the typical 'bell shaped curve' to a plateau with a significant reduction in the maximal concentration (C_{max}) (van Maarseveen and van Zuilen, 2013). This phenomenon is not observed in those taking PI-sparing cART where total exposure for both CNIs is lower than AUCs observed in the general population (median [IQR] respectively, CsA 862 [744–1131] vs 7000–9000 and Tac 2170 [936–3261] vs 2000–5000 ng*hr/mL/mg/kg at weeks 2 to 12 post-KT) (Frassetto et al., 2013). In our cohort

pharmacokinetic studies were performed in 6 patients taking Tac and PI-sparing cART (**Appendix G** - not included in data analyses), we observed somewhat similar AUCs compared to those reported by Frassetto et al (2014).

By contrast to the increased total exposure AUC, time to maximal concentration (T_{max}) of Tac was delayed in those taking PI-containing cART compared to those on PI-sparing cART specifically NNRTIs (6 vs 2 to 3 hours). In those taking CsA, T_{max} was similar for both cART groups (2 to 3 hours) (Frassetto et al., 2014). In the general population T_{max} for both CNIs is 2 to 3 hours (Schiff et al., 2007). The delay in T_{max} for those taking Tac/PI-containing cART suggests a slower rate of absorption (Kuypers et al., 2004). Additionally, the extension of Tac half-life by PIs in turn prolongs the time to achieve steady state concentration (T_{ss}). The administration of a loading dose may assist in achieving T_{ss} quicker provided the kinetics remains linear. In a small PK study to determine an optimal loading dose for Tac when co-administered with PI-containing cART observed wide interpatient variability for doses ranging from 1 to 7 mg (van Maarseveen and van Zuilen, 2013). The PK studies performed with 1mg loading dose in three patients demonstrated some peak concentrations that were within therapeutic range (8 to 15ng/ml) though after 96 hours concentrations were subtherapeutic. The 2mg loading dose demonstrated much higher peaks similar to those observed in the HIV negative population (~20 to 25ng/ml) (Hardinger et al., 2004b)). However, subsequent concentrations achieved were not reported therefore unable to ascertain if target concentrations were sustained at a dosing interval of 168 hourly. The much higher doses of 6.5 to 7mg resulted in significantly high peaks that were sustained 96 hours post-dose. This was also the case in our cohort where supratherapeutic concentrations were sustained in some instances up to one

month post-dose even with Tac discontinuation (data not shown). Though the van Maarseveen (2013) study was conducted in the pre-transplant setting which limited inferences drawn from their conclusions. Furthermore, their patients were taking combined PI/r and NNRTI cART regimens which results in large variances in total drug exposure (Frassetto et al., 2014). In addition, single oral dose pharmacokinetic studies differ from multiple oral dosing due to the cumulative drug absorption (Rowland et al., 2011).

Besides total drug exposure, it is uncertain whether C_{trough} is the best time point for optimal therapeutic drug monitoring. The Frassetto et al (2014) study suggests that over the course of time post-transplantation C_{trough} correlates with AUC in those taking Tac and C_4 correlates better with AUC than C_0 or C_2 in those taking CsA.

Perhaps for the HIV/KT population employing more stringent monitoring strategies may alleviate the high allograft rejection rates. In support of this notion and to complicate matters further, time dependent changes to the clearance and oral bioavailability have been observed for both CsA and Tac when co-administered with various cART (Frassetto et al., 2013). For example, in subjects taking CsA and efavirenz antiretroviral drug observed ~30% increases in apparent oral bioavailability and decreased apparent oral clearance over time. On the contrary, those taking Tac/EFV observed an increase in both apparent bioavailability and clearance over time requiring a Tac dose reduction over time to maintain therapeutic concentrations. Subjects taking nevirapine did not exhibit the same decline in CsA oral clearance over time (Frassetto et al.,

2013). Interestingly, the same authors observed increases in oral CsA bioavailability over time in those subjects taking PI-containing cART in one study (Frassetto et al., 2003) and no time-dependent alterations to the bioavailability in a subsequent study (Frassetto et al., 2013). This reiterates the unpredictability of changes to the pharmacokinetic parameters of CNIs irrespective of ART choice.

The strength of this study is near complete sample that was well matched except for cART choice. The descriptive nature of this study provides some insight into the challenges of achieving and maintaining CNI drug concentrations in clinical practice when managing HIV/KT patients. The representation of the proportions of CNI drug concentrations that are above, below or within target range provides a more complete picture of the actual concentrations achieved compared to mean (SD) represented in the previously reported HIV/KT studies (Frassetto et al., 2005, Stock et al., 2010a, Frassetto et al., 2013, Frassetto et al., 2014). The variability observed may explain the poor allograft outcomes observed in this population. A further limitation is the possible use of different CNI formulations both between patients and within individuals over the study period. The utilisation of the pre-KT CNI trial as a dose finding strategy may have resulted in certain patient groups post-KT achieving target concentrations much quicker. Futhermore in the early years of HIV/KT circa 2005, there may have been an unawareness of CNI and cART drug interactions therefore extremely supratherapeutic concentrations may have skewed results. Finally, the effect of other covariates gender (Min et al., 2000) that may have caused variations in CNI drug exposure.

5.5. Conclusion

This study describes the challenges of achieving and maintaining therapeutic CNI C_{trough} in clinical practice over the first year post-transplant in HIV kidney transplant recipients. The co-administration of antiretroviral drugs with calcineurin inhibitors results in unpredictable drug exposure which is multifactorial but also highlights the challenges of managing these drug interactions. Use of integrase inhibitors to avoid the CNI and antiretroviral drug interactions is one way for optimal CNI exposure. However, where use of INI based cART is not possible, there are a few approaches to determining the optimal CNI dose when co-medicated with PI-containing cART especially. One approach is the use of a pre-transplant CNI trial. The current dataset was not robust to test this approach especially for those on tacrolimus and PI-containing cART combination.Another approach, if calcineurin inhibitors exhibit linear kinetics when combined with PI-containing cART, is the use of standardised dosing to limit superexposure e.g. 0.5 to 1mg/week of tacrolimus initiating dose with close therapeutic drug monitoring. However, with extended dosing intervals it may take longer to reach steadystate. One way to overcome the extended time to steadystate is by use of a loading dose. van Maarseveen (2013) data suggests a dose between 1 to 2mg would be required to achieve peak tacrolimus concentrations between 10 to 30ng/mL. The availability of liquid tacrolimus formulations (e.g. Modigraf® (AstellasPharma, 2015)) may also offer the advantage of administering smaller doses more frequently. However, a prospective pharmacokinetic study to determine an optimal approach of CNI dosing with PI-containing cART is warranted to corroborate these findings.

Chapter 6. Mycophenolate Therapeutic Drug Monitoring (TDM) in HIV-Positive Kidney Transplant Recipients

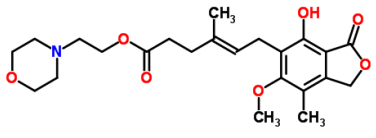
6.1. Introduction

Mycophenolate pharmacology

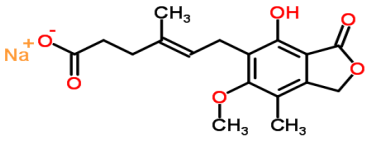
Mycophenolate (MMF) was originally discovered in the late 19th century from *Penicillium brevicompactum* (Franklin and Cook, 1969, Eugui et al., 1991, Jeong and Kaplan, 2007). MMF is a potent and reversible inhibitor of inosine monophosphate dehydrogenase (IMDH), an enzyme that is involved in purine DNA synthesis. This mode of action prevents the proliferation of T cell lymphocytes and antibody formation by B cells. It also inhibits the recruitment of leukocytes to inflammatory sites (Hardman et al., 1996a). These immunosuppressive and anti-inflammatory processes are necessary for the prevention of allograft rejection in kidney transplantation. Mycophenolate proved ineffective as a single immunosuppressive agent rather as complementary drug to the combined use of calcineurin inhibitors and prednisolone for the prevention of allograft rejection (Jeong and Kaplan, 2007).

Mycophenolate is available in two salt forms, mycophenolate mofetil and mycophenolate sodium, chemical structures shown in **Figure 32** (chemistry, 2014). Both forms when hydrolysed form the active metabolite, mycophenolic acid (MPA). Mycophenolate therapeutic drug monitoring involves measuring MPA concentrations in plasma (Staatz and Tett, 2007).

Figure 32: Mycophenolate Chemical Structure



Mycophenolate mofetil
Molecular Formula: $C_{23}H_{31}NO_7$

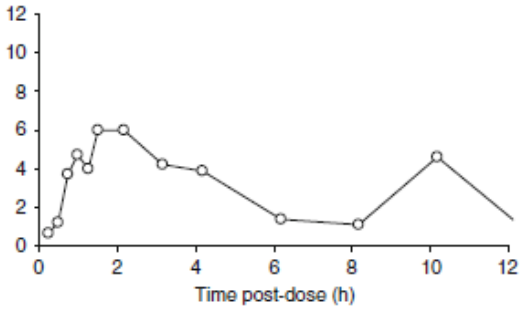


Mycophenolate sodium
Molecular Formula: $C_{17}H_{19}NaO_6$

Mycophenolate drug disposition in kidney transplant recipients

Mycophenolate is extensively absorbed in the gastrointestinal tract with 72% to 94% oral bioavailability (Staatz and Tett, 2007). MMF then undergoes glucoronidation by UDP-glucuronosyltransferase enzymes in the gastrointestinal tract, liver and possibly kidney before being excreted primarily into the urine and bile in its inactive form (mycophenolic acid glucoronide (MPAG))(Sweetman, 2011, [PharmGKB], 2014) (Moreno et al., 2008, Sweetman, 2011, [PharmGKB], 2014). MPAG in the bile undergoes de-glucoronidation by bacterial enzymes back into MPA in the gastrointestinal tract before being reabsorbed. This enterohepatic recycling process is demonstrated in the delayed peak 6 to 12 hours after oral administration (see **Figure 33**) (Bullingham et al., 1998, Jeong and Kaplan, 2007). However, mycophenolate drug interactions have been known to interfere with the enterohepatic recycling process. There is evidence to suggest that ciclosporin inhibits enterohepatic recycling of MPAG thereby increasing mycophenolate dosing requirements in order to achieve adequate therapeutic MPA plasma concentrations (Cremers et al., 2005).

Figure 33: Mycophenolic Acid Plasma Concentration Time Profile



Graph showing mycophenolic acid plasma concentration time profile demonstrating enterohepatic recirculating seen following oral mycophenolate mofetil administration (Staatz and Tett, 2007).

There is large inter- and intra-patient variability of exposure to MPA in transplant recipients that is not entirely understood, and many factors may also contribute, including food, race, renal function, albumin level, delayed graft function, concomitantly administered interacting drugs and polymorphisms of metabolic enzymes and multidrug resistance proteins (Staatz and Tett, 2007, Grinyo et al., 2009).

Mycophenolate Therapeutic Drug Monitoring

Over recent years, there has been much debate on the utility of mycophenolate therapeutic drug monitoring in solid organ transplantation. Therapeutic drug monitoring aims to optimise therapy by individualised dosing and avoid drug toxicity. In solid organ transplantation, not achieving therapeutic mycophenolate dosing can be detrimental to the allograft in preventing rejection. However, emerging evidence deterred the benefits of MPA TDM on the basis of lack of cost-effectiveness and opted instead for dose adjustment guided by MMF-associated haematological or gastrointestinal toxicity (Kuypers et al., 2010). Clinical reviews were performed to evaluate the scientific evidence on TDM of MPA in solid organ transplantation (Jeong and Kaplan, 2007, Knight and Morris, 2008, Knight et al., 2009, Kuypers et al., 2010) and found that strong evidence was lacking to demonstrate

i. relationship between MPA exposure and allograft rejection or graft loss (van Gelder et al., 2008, Gaston et al., 2009)
ii. relationship between MPA exposure and MMF-associated toxicity (Le Meur et al., 2007, van Gelder et al., 2008, Gaston et al., 2009)

iii. defined target MPA concentrations, both 12-hour trough (C_{trough}) and total exposure (AUC), that determined clinical efficacy and toxicity (Kuypers et al., 2010)

iv. strategies to achieve therapeutic target MPA concentrations in clinical practice (Le Meur et al., 2007, Budde and Glander, 2008, Gourishankar et al., 2010)

v. cost-effectiveness of monitoring patients when they achieve steady state therapeutic target MPA concentrations (Kuypers et al., 2010)

Although in certain patient groups the role of MPA TDM was found beneficial particularly in view of the wide inter/intra-patient variability of MMF exposure (Kuypers et al., 2010). For example, patients with high immunological risk where achieving and maintaining therapeutic MPA concentrations is critical in preventing allograft rejection (Kuypers et al., 2009, van Gelder et al., 2010). van Gelder et al (2010) defined those of high immunological risk as those with delayed graft function, re-transplants, panel reactive antibodies >15%, four or more human leukocyte antigen mismatches, or those of black ethnicity. In their study, those with high immunological risk (n=549) that achieved therapeutic MPA AUC had a lower rate of allograft rejection compared to those that achieved lower MPA AUC concentrations in the first month post-KT (14.3% vs 7.8%, p=0.025). In the low immunological risk group, no differences in allograft rejection rates were observed irrespective of MPA AUC concentrations (5.7% vs 4.5%).

HIV infected kidney transplant recipients are considered to be of high immunological risk due to a combination of factors discussed in previous chapters. To summarise these factors briefly: there is a high proportion of HIV infected KT recipients of black ethnicity (74%, n=35 (Gathogo et al., 2014); 69%, n=150 (Stock et al., 2010a)); a high incidence of delayed graft function in HIV/KT recipients has been observed especially in those who receive allografts from deceased donors (52%, n=36 (Mazuecos et al., 2013); 46% for deceased donor recipients, n=150 (Stock et al., 2010b)); and high incidences of allograft rejection in the first year post-KT (44%, n=35 (Gathogo et al., 2014); 31%, n=150 (Stock et al., 2010b)). Furthermore, the delicate balance of immunosuppression in this cohort is crucial for the prevention of latent viral reactivation and HIV disease progression. Although cART have somewhat improved the incidence of certain opportunistic infections in HIV infection (Nelson et al., 2011), there is an increased risk of latent virus reactivation post-KT with the use of immunosuppressive therapy. In addition, post-HIV/KT immunosuppression could be further complicated by the co-medication of cART with immunosuppressant drugs resulting in profound drug interactions. Co-administration of mycophenolate and antiretroviral drugs that inhibit or induce glucuronidation, e.g. some protease inhibitors and non-nucleoside reverse transcriptase inhibitors, could potentially alter MPA concentrations (LHPG, n.d). Although clinical evidence of these cART-MPA drug interactions is lacking. An in vivo study including indinavir did not demonstrate any alterations of MPA concentrations (Sankatsing et al., 2004b). In the same study, there was an incidental finding of increased nevirapine clearance (MMF (n=9) vs No MMF (n=8) clearance (CL/F (L/h)) 3.25 (2.88–3.70) vs. 2.83 (2.43–3.34), p=0.04) thought to be induced by MPA however; the mechanism is unknown. MPA can

also potentially increase the intracellular concentrations of abacavir by depleting intracellular deoxyguanosine triphosphate (dGTP). However, the intracellular concentrations of abacavir or its active form, carbovir triphosphate, have not been altered when co-administered with mycophenolate (Sankatsing et al., 2004b). Mycophenolate has also been demonstrated to inhibit the renal transporters organic anion transport (OAT) - OAT1/OAT3 which may reduce elimintation of tenofovir disoproxil fumarate (tenofovir DF) (Burckhardt and Burckhardt, 2011). **Table 33** summarises the drug interactions between mycophenolate and antiretroviral drugs available in the UK. Aside from drug interactions with cART, interactions occur between IS drugs. An example of this has been demonstrated between calcineurin inhibitors and mycophenolate. Increased MMF exposure has been demonstrated when co-medicated with ciclosporin (Hubner et al., 1999, Vidal et al., 2000, Pou et al., 2001, Grinyo et al., 2009, Naito et al., 2009). For example, one study demonstrated that despite higher doses of MMF in the ciclosporin group (n=16) there was a 50% reduction in MPA C_{trough} concentrations compared to tacrolimus group (n=14) [mean (SD) CsA, Tac respectively: doses 2.8±1.2 vs 0.07±0.01 mg/kg/day; 125.9±37.4 vs 7.7±2.8 µg/L] (Gerbase et al., 2003).

This chapter aims to evaluate the utility of mycophenolate TDM in HIV kidney transplant recipients by comparing concentration guided MMF dosing to MMF dosing modifications following adverse events (ADEs).

Table 33: Antiretroviral / Mycophenolate Drug Interaction Table

PI	DI w/ MMF	NNRTI	DI w/ MMF	NRTI	DI w/ MMF	Other	DI w/ MMF
Atazanavir	X	Delavirdine	X	Abacavir	X	Dolutegravir	X
Cobicistat (with ATV or		Efavirenz	X	Didanosine		Elvitegravir/cobicistat	X
Darunavir	X	Etravirine		Emtricitabine		Maraviroc	X
Fosamprenavir	X	Nevirapine	X	Lamivudine		Raltegravir	X
Indinavir	X	Rilpivirine		Stavudine			
Lopinavir	X			Tenofovir-	X		
Nelfinavir	X			Zidovudine	X		
Ritonavir	X						
Saquinavir	X						

Key: PI, Protease Inhibitors; DI w/ MMF, Drug interaction with mycophenolate; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor. X – Theoretical or clinical evidence of drug interaction.

Purpose of study

The main purpose of this chapter is to evaluate the clinical utility of mycophenolate therapeutic drug monitoring in HIV kidney transplantation. With a focus on the first 12 months post-kidney transplant, these analyses will assess whether concentration guided mycophenolate dosing offers a better strategy compared to MMF dosing modifications following adverse events.

Primary Aim

To evaluate the utility of mycophenolate therapeutic drug monitoring (TDM) in HIV kidney transplantation (HIV/KT). To address this aim the following hypotheses were addressed

1.1 Hypothesis (H_0) Stratified *a priori* by mycophenolate TDM, there are no differences in the rate of the first mycophenolate discontinuation between groups in the first year post-HIV/KT

1.2 Hypothesis (H_0) Stratified *a priori* by mycophenolate TDM, there are no differences in the rate of MMF associated treatment limiting latent viral reactivations (CMV, EBV and BK reactivation) between groups in the first year post-HIV/KT

1.3 Hypothesis (H_0) Stratified *a priori* by mycophenolate TDM, there are no differences in the rate of MMF associated treatment limiting cytopenias between groups in the first year post-HIV/KT

1.4 Hypothesis *(H_0)* Stratified *a priori* by mycophenolate TDM, there are no differences in the rate of allograft rejection between groups in the first year post-HIV/KT

Secondary Aims

Aim 1: To describe mycophenolate dosing in HIV/KT in the first 12 months post-transplant

Aim 2: To describe mycophenolate 12h C_{trough} plasma concentrations in HIV/KT with mycophenolate TDM over the first year post-transplant

Aim 3: Stratified *a priori* by mycophenolate TDM, describe the host/graft survival

Aim 4: To identify factors associated with (1) MMF discontinuation (2) Adverse events/viral reactivation (3) Acute graft rejection

Aim 5: To explore the possible drug interactions in those co-prescribed abacavir and mycophenolate.

Definitions

Clinical efficacy of mycophenolate use was defined by the prevention of allograft rejection in the first year post-transplant. Allograft rejection was histologically confirmed on biopsy as described in detail in Chapter 4.

Haematological adverse events were restricted to clinician reported treatment limiting cytopenias. The treatment limitation was defined as mycophenolate treatment that was interrupted/delayed or discontinued due to the mycophenolate induced cytopenias. The specific cytopenias included neutropenia and leukopenia. Although haematological ADEs were clinician reported, local centre protocols commonly defined leukopenia as having a total white blood cell (WBC) count of less than 3,000-4,000 cells/μL; neutropenia was commonly defined as having a neutrophil count of $<0.5 \times 10^9$ /L.

Latent viral reactivation was clinician reported and verified by laboratory viral load measurements. Latent viruses included herpes simplex viruses 1 and 2, varicella zoster virus (VZV), human herpes viruses (HHV) 6, 7, and 8, Epstein - Barr virus (EBV), polyomaviruses - BK and JC viruses, and cytomegalovirus (CMV). Viral load detection limits and thresholds were determined at study centres according to local protocols. For the purposes of these analyses latent viral reactivation was defined as any viraemia that resulted in MMF dose adjustment or discontinuation and/or required antiviral therapy where applicable (e.g. valganciclovir to treat CMV or acyclovir for HSV).

Mycophenolate therapeutic drug monitoring was performed by measuring plasma concentrations of the active metabolite mycophenolic acid. MPA trough plasma concentrations (MPA C_0) were defined by concentrations determined at 12 hours or 6 hours post-dose where dose frequencies were twice or four times daily respectively. Analytical assays used to measure MPA C_0 varied between centres and during the study period. Although, the most commonly used were Enzyme Mediated Immuno-Technique (EMIT), liquid chromatography with tandem mass-spectrometric detection (LCTMS) or Roche enzyme inhibition assays. Comparisons between immunoassays has been performed and MPA results by LCTMS were ~20% lower than using the EMIT assay (Shipkova et al., 2000, Weber et al., 2002a, van Gelder et al., 2009). This is due to the cross-reactivity in the EMIT assay of the MPA metabolite MPA acyl glucuronide (MPAG) therefore requiring higher target concentrations. MPA C_0 concentration efficacy was defined by local protocols. Therapeutic target concentrations ranged from 1 – 3.5mg/L (LCTMS) or 1.3 – 4.5mg/L (EMIT) (Weber et al., 2002a, Kuypers et al., 2010). For the purposes of this analyses target range of 1 – 3.5mg/L was used as LCTMS immunoassay was most commonly used. Furthermore, immunoassays used for each MPA concentration was not reported only overall immunoassay choice per centre was reported.

6.2. Method

Study Design

The full details of the study methods have been previously described in Chapter 3 (see pages 109 to 113). For this chapter, enrolled patients were stratified *a priori* by MMF TDM vs no TDM post-transplantation. Baseline patient characteristics were described as follows

a. Recipient characteristics
    i. Demographics: age, gender, ethnicity
    ii. Aetiology of kidney disease
    iii. HIV parameters: CD4 count, cART regimen
    iv. Co-morbidities: diabetes, hypertension
    v. HBV/HCV/CMV serology
b. Graft characteristics
    i. Allograft type & HLA mismatch
    ii. Donor/recipient CMV status mismatch

Inclusion criteria

In addition to the overall study inclusion/exclusion criteria described in Chapter 3, patients were included in these analyses if

a. Mycophenolate was included in post-HIV/KT immunosuppressant drug therapy management
b. Data were available for
    i. mycophenolate doses, formulations, start/stop dates, reasons for discontinuation
    ii. MMF associated adverse events (treatment limiting cytopenias (neutropenia and leukopenia) and latent viral reactivations (e.g. cytomegalovirus, BK virus, Epstein-Barr virus, herpes simplex virus))
    iii. Post-transplant allograft outcomes - function and biopsy proven allograft rejection
    iv. > 3 serial post-transplant mycophenolate trough concentrations

Exclusion criteria

Patients were excluded if

a. Post-transplant immunosuppressant drug therapy excluded mycophenolate e.g. calcineurin inhibitor monotherapy or azathioprine containing IS therapy
b. <3 mycophenolate concentrations available post-transplant
c. Mycophenolate concentrations measured post-dose or as part of pharmacokinetic studies (AUC)
d. Patients with insufficient/missing/no data

Study Analysis

To address the study hypothesis first descriptive analyses were used to summarise mycophenolate use, mycophenolate concentrations and post-transplant allograft outcomes and adverse events. Secondly, stratified *a priori* by mycophenolate TDM comparisons were made between groups as outlined below. Finally, further analyses were performed to identify factors associated with mycophenolate discontinuation, allograft outcomes and adverse events. Analyses were limited to the first 12 months post-transplant.

Mycophenolate Use in HIV/KT

Descriptive analyses of mycophenolate use in HIV/KT recipients that met the study criteria were outlined as follows

a. Proportion of subjects on MMF at day 1, at the end of weeks 1 and 2, and at the end of months 1, 2, 6 and 12.
b. Dose at day 1 and at the end of weeks 1 and 2, and at the end of months 1, 2, 6 and 12. Additional information included MMF - dosing interval, dose changes, discontinuations and reasons for discontinuation/dose reduction in the first year post-KT.
c. Stratified *a priori* by mycophenolate TDM, comparative analyses of MMF doses at weeks 1 and 2, and the end of months 1, 2, 6 and 12.
d. Stratified *a priori* by mycophenolate TDM, comparative analyses of MMF doses at weeks 1 and 2, and end of months 1, 2, 6 and 12 for those that had BPAR vs those that remained rejection free in the first year post-KT.
e. Stratified *a priori* by MMF TDM, descriptive analyses were performed for reasons for first MMF dose reductions.

Mycophenolate concentrations

Descriptive analyses of MPA C_0 concentrations were outlined as follows

a. First measured concentration
b. Concentrations at end of weeks 1 to 52 post-KT
c. Concentrations below/within/above the target range at end of weeks 1 to 52 post-KT
d. Relationship of fixed covariates abacavir, cART choice (PI-containing vs PI-sparing), ethnicity, allograft rejection and CNI choice (tacrolimus and ciclosporin) with MPA C_0 concentrations at end of weeks 1 and 2, and end of months 1, 2, 6 and 12 months post-KT

Mycophenolate discontinuation and adverse events

Stratified *a priori* by MMF TDM analyses were performed as follows

a. Cumulative incidence of MMF discontinuation (KM curves)
b. Cumulative incidence of adverse events
    i. Cumulative incidence of clinician reported cytopenias (neutropenia, leukopenia)
    ii. Cumulative incidence of latent viral infections (CMV, EBV and BK reactivation)
    iii. Cumulative incidence of death/graft survival
    iv. Cumulative incidence of acute graft rejection
c. Descriptive analyses for reasons for MMF discontinuation

Analyses were limited to first occurrence of events i.e. time to first MMF discontinuation, first post-KT infection and first allograft rejection episode.

Gastrointestinal adverse events were excluded from these analyses due to the high prevalence of non-infectious diarrhoea associated with HIV and antiretroviral therapy observed in HIV-positive patients (Macarthur, 2013). A large study from the United Kingdom reported the prevalence of diarrhoea in HIV-positive patients as 67% and 20% in cART treated vs treatment naïve respectively (n=778) (Harding et al., 2010). It would have been difficult to ascertain whether gastrointestinal ADEs were mycophenolate induced or due to HIV infection or cART.

Factors associated with mycophenolate discontinuation and post-transplant outcomes/ADE

This section of the analyses aims to identify factors associated with

a. MMF discontinuation
b. Latent viral infections
c. Haematological adverse events

Study Assumptions and Confounding factors

Mycophenolate acid trough plasma concentrations reported were assumed to be true MPA trough concentrations (C_0). 100% mycophenolate adherence was assumed for all enrolled HIV/KT recipients.

Interpretation of MPA concentrations was limited by the confounding factors listed below.

- Polypharmacy to include drugs that potentially interact with mycophenolate
- Within/between centre MPA immunoassay sensitivity and variability over the study period
- Variations within/between centres of the MPA target concentrations
- Switching mycophenolate formulations to generic preparations or other formulations (e.g. oral suspensions or intravenous infusions)

Sample size limited analyses to include adjustments for confounding factors.

Statistical analysis

Prior to performing analyses, the distribution of all available mycophenolate doses and MPA concentrations were assessed using graphical methods to include histogram and skewness/kurtosis tests to test for normality. Normally distributed data were represented as mean (SD) and comparison of means using t-test statistical tests. Positively skewed data were represented as median (IQR) and comparisons made using Wilcoxon-rank sum (Mann-Whitney) statistical test. Statistical significance was considered if p value <0.05.

Baseline recipient characteristics and reasons identified for MMF first dose reductions/discontinuations were analysed using univariate methods stratified *a priori* by MMF TDM vs No TDM. Statistical significance for comparing: proportions was tested using two-sided chi-squared test; medians was tested with Wilcoxon rank-sum and T-tests for means.

Univariate cox proportional hazard regression analyses were used to identify factors associated with latent viral infection, haematological ADEs and first MMF discontinuation in the first year post-transplant. Factors that demonstrated statistical significance were included in multivariate regression analyses.

Analyses of mycophenolate doses at day 1, week 1, 2, and months 1, 2, 3, 4, 6, and 12 post-KT were performed using a two-way analysis of variance (ANOVA), if data demonstrated normal distribution, to analyse differences between group means. Variables tested were (1) calcineurin inhibitor choice (2) mycophenolate TDM (3) CNI and MMF TDM interaction.

Cumulative incidence of patient/graft survival, allograft rejection, MMF-associated haematological ADEs and latent viral infections were estimated using Kaplan-Meier methods and significance tested with log rank test.

Stratified *a priori* by MMF TDM, comparative analyses of allograft function determined by eGFR (CKD-EPI) at selected time points were performed using Wilcoxon-rank sum (Mann-Whitney) statistical test.

A multi-level mixed effect linear regression model was used to analyse repeated measures data, i.e renal graft function measured at days 30, 60, 120, 180 and 365 post-KT. This mixed effect model was performed to examine whether there was a significant difference ($p < 0.05$) in change of graft function from baseline to 1 year post-KT for patients that had MMF TDM compared to those that did not. The association of MMF TDM and the slopes of graft function versus time post-transplant were also examined using mixed-effect models allowing for a random intercept and slope. The analysis was performed using the *xtmixed* command in STATA (version 12.0). Graft function was expressed as eGFR calculated using the CKD-EPI equation.

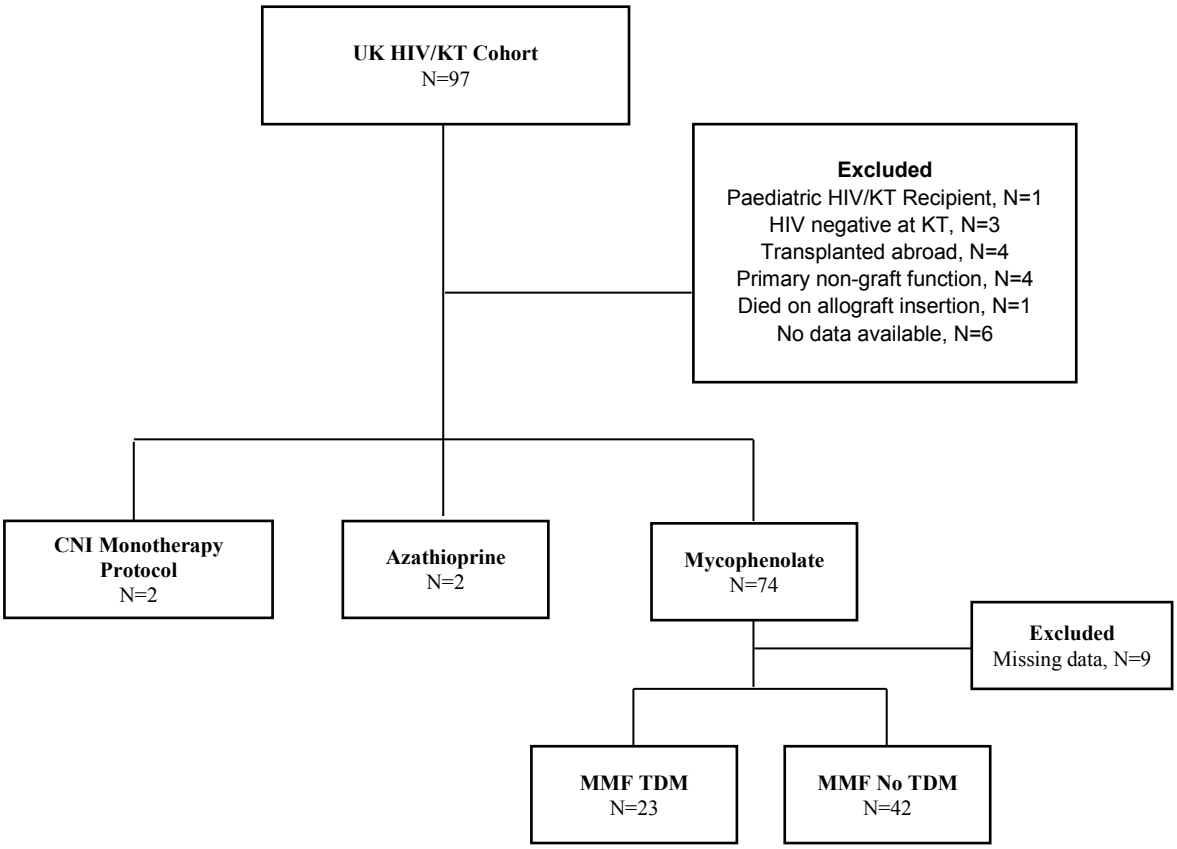
6.3. Results

Patient disposition

Between 2005 and December 2013, 97 HIV Kidney Transplant recipients were identified. Those that did not meet the study inclusion criteria (N=23) included: one patient less than 18 years of age; four transplanted abroad (India, Belgium, Berlin and USA); three that acquired HIV post-transplantation; one patient who died during KT; four with primary non-graft function; two that received CNI monotherapy; two received azathioprine; and six that had no data. The six patients were transplanted at Oxford Radcliffe hospital (n=4), Birmingham (n=1) and Manchester (n=1), refer to **Figure 34** for full patient disposition. All were referrals from external HIV centres (unknown) and received post-transplant follow-up at their base hospitals. Of the 74 patients that were taking mycophenolate, 9 were excluded from further analyses the reasons were as follows: At KT only 1 patient was taking mycophenolate sodium (Myfortic®) whereas the remaining patients took mycophenolate mofetil (Cellcept®) preparations; and 9 with no data on mycophenolate dosing, MMF drug concentration monitoring or post-KT adverse events (Manchester n=7; Edinburgh n=1; Bart's & the London n=1).

Analyses in this chapter includes those taking mycophenolate with available data for n=65, 23 TDM vs 42 No TDM. During the study period, four transplant centres performed MMF TDM. 493 MPA concentrations were performed in 23 HIV/KT recipients in the first year post-KT. The median (IQR) MPA concentrations per subject were 23 (10, 27). Two patients that had <3 MPA concentrations available were excluded from full mycophenolate drug concentration analyses. However, these patients were included in statistical analyses where MMF TDM was categorical (Yes/No).

Figure 34: Patient disposition for UK HIV/KT cases stratified by those with Mycophenolate TDM



Patient characteristics

The MMF TDM vs. No TDM groups were well matched for baseline patient characteristics except for gender (p=0.02) (**Table 34**). Of 65 with available data included in the analyses, 43 were male, 51 of black ethnicity with median (IQR) age at KT of 44 (38, 51) years. The Median (IQR) follow-up period was 29.7 (12.6, 51.6) months.

Table 34: Baseline patient characteristics at kidney transplantation according to Mycophenolate TDM status

Characteristics		**MMF TDM N = 23**	**MMF No TDM N = 42**	**P value**
Age, median(IQR)	Years	44(37, 50)	44 (39, 52)	0.47
Gender, n (%)	Male	11 (48)	32 (76)	**0.02**
Ethnicity	Black	18 (78)	33 (79)	0.97
Cause of ESKD	HIVAN	12 (52)	19 (45)	0.59
HIV parameters				
CD4 count, median (IQR)	Cells/mm^3	364 (267, 527)	421 (299, 566)	0.32
Co-morbidities				
Diabetes		3 (13)	6 (14)	0.86
Hypertension		22 (96)	38 (90)	0.64
Hepatitis B co-infection, n (%)		3 (13)	5 (12)	0.89
Hepatitis C co-infection, n (%)		1 (4)	3 (7)	0.64
Graft characteristics				
Allograft type	Cadaveric	16 (70)	26 (62)	0.54
	Living	7 (30)	16 (38)	
Delayed graft function, n (%)		5 (22)	10 (24)	0.77
HLA mismatch, median(IQR)		3 (2, 3)	3 (2, 4)	0.57
Donor/Recipient CMV mismatch status, n (%)	D+/R-	2 (9)	2 (5)	0.53

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test, comparing proportions (%), two-sided chi-squared test. Statistically significant ($p < 0.05$)

Table 35: Baseline immunosuppression and antiretroviral drug therapy stratified by MMF TDM

	MMF TDM N = 23	MMF No TDM N = 42	P value
Mycophenolate initiation at KT, median(IQR)			
Dose [g/day]	1.5 (1.5, 2)	2 (2, 2)	**0.0009**
Weight based dose [g/kg/day]‡	0.024 (0.019, 0.031)	0.028 (0.025, 0.032)	**0.03**
Dosing interval [no. per day]	2 (2, 2)	4 (2, 4)	**0.0000**
CNI Choice at KT, n (%)			
Ciclosporin	8 (35)	23 (55)	0.12
Tacrolimus	15 (65)	19 (45)	
Antiretroviral therapy at KT, n (%)			
Abacavir containing cART (Yes)	8 (35)	16 (38)	0.79
PI/r based cART	12 (52)	13 (31)	0.09

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test; comparing proportions (%), chi-squared test. Statistically significant ($p < 0.05$)

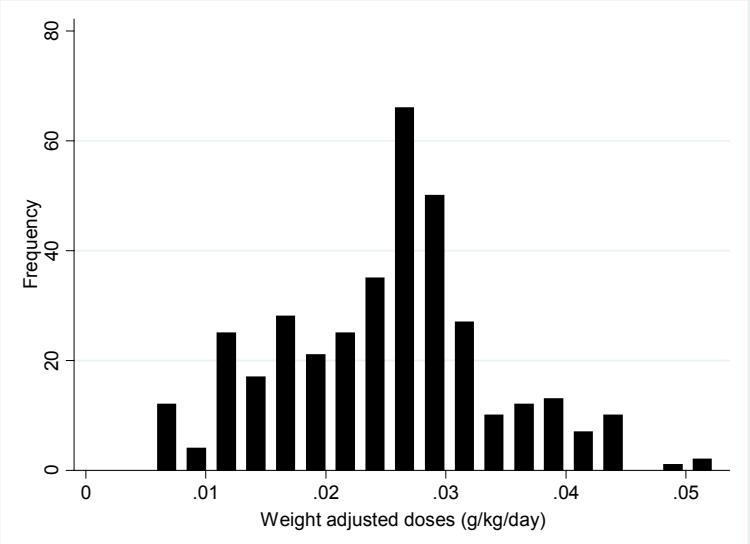
‡Weight unavailable for 1 male patient. Average weight of adult male patient = 70kg assumed.

Key: CNI – calcineurin inhibitor; PI/r – ritonavir boosted; cART – combinational antiretroviral therapy

Mycophenolate Dosing

The overall mycophenolate doses were not normally distributed (see **Figure 35**) therefore, data were presented as median (IQR). Initial mycophenolate doses used overall were similar to the general kidney transplant population (2 (1.5, 2) vs 2 g/day (RocheProductsLtd, 2006), respectively). The overall weight adjusted dose was 0.03 (0.02, 0.03) g/kg/day. Those that had MMF TDM used significantly lower initiating doses compared to those without TDM (1.5 (1.5, 2) vs 2 (2, 2) g/day, respectively p=0.0009) (see **Table 35**). This could be explained by the differences in transplant protocols where one centre recommended pre-emptive MMF dose reductions of 1.5g/day to compensate for the known tacrolimus and mycophenolate interaction (n=15) (Hubner et al., 1999, van Gelder et al., 2000, Miller and Williams, 2009). 12-hourly MMF dosing interval was most commonly used in the TDM group compared to the no TDM group, median (IQR) 2 (2, 2) vs 4 (2, 4) (p=0.0000). Although in later years of the study period (2010 to 2013), dosing interval of four times daily was increasingly used by centres as a strategy to avoid MMF-associated gastrointestinal adverse effects (e.g. diarrhoea).

Figure 35: Histogram of overall mycophenolate dosing irrespective of TDM stratification

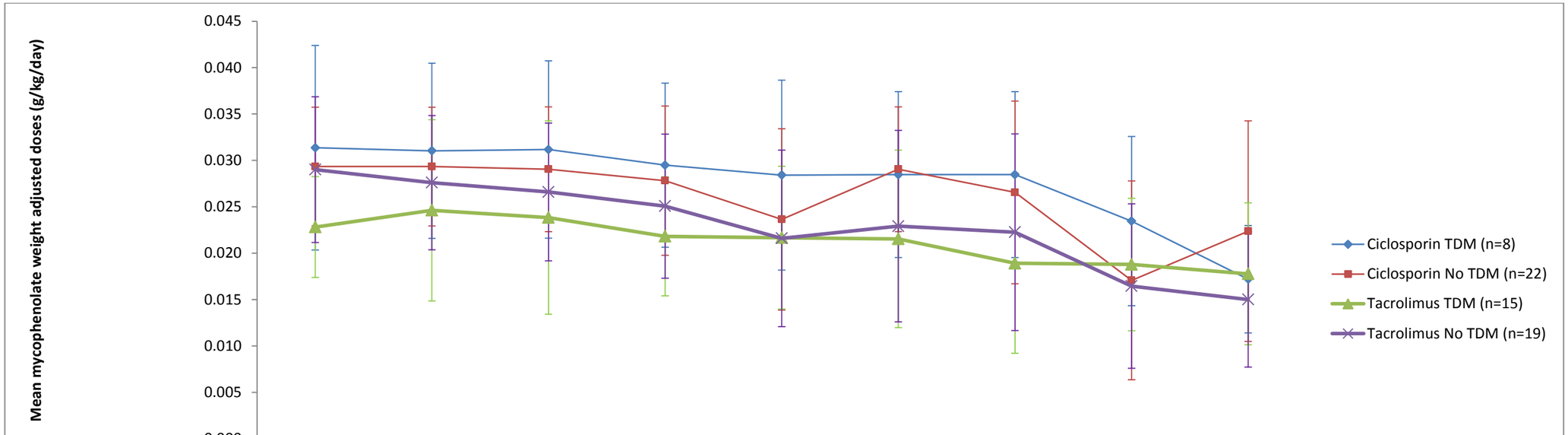


Test for normality based on skewness: Skewness/Kurtosis tests for Normality - Skewness = 0.21, Kurtosis = 2.97, P value = 0.46. Data were normally distributed at least at the 46% level. P value indicates that it is not significantly different from the kurtosis of a normal distribution at the 5% significance level therefore we cannot reject the hypothesis that mycophenolate doses in the first year post-KT are normally distributed.

Mycophenolate dose adjustments was common in the first year post-KT with 68.8% (n=44) having a median (IQR) 2 (1.5, 4) number of dose changes (analysis censored at MMF discontinuation, death or date last clinic visit up to 1 year). There was a similar proportion of patients that had MMF dose adjustments in the TDM vs No TDM groups (70%, n=16 vs 68%, n=28, p=0.87). Of the 44 that had MMF dose adjustment irrespective of TDM monitoring, 41% (n=18) had a dose reduction during 12 month follow-up for majority MMF-associated latent viral infection or haematological ADRs, further details to be discussed.

Analyses of MMF doses stratified by abacavir containing cART vs abacavir free cART observed no statistical differences (data not shown).

Figure 36: Mean (+/-SD) Mycophenolate doses in the first year post-KT



	Day 1	Week 1	Week 2	Month 1	Month 2	Month 3	Month 4	Month 6	Month 12
Ciclosporin TDM (n=8)	0.031	0.031	0.031	0.029	0.028	0.028	0.028	0.023	0.017
Ciclosporin No TDM (n=22)	0.029	0.029	0.029	0.028	0.024	0.029	0.027	0.017	0.022
Tacrolimus TDM (n=15)	0.023	0.025	0.024	0.022	0.022	0.022	0.019	0.019	0.018
Tacrolimus No TDM (n=19)	0.029	0.028	0.027	0.025	0.022	0.023	0.022	0.016	0.015

	DF	Sum of Squares	Mean Square	F Value	P Value
Calcineurin inhibitor Choice	1	.002007677	.002007677	23.98	**0.0000**
Mycophenolate TDM	1	2.1332e-06	2.1332e-06	0.03	0.8733
MMF TDM # CNI Choice Interaction	1	.000089339	.000089339	1.07	0.3024
Model	3	.002134115	.000711372	8.50	**0.0000**

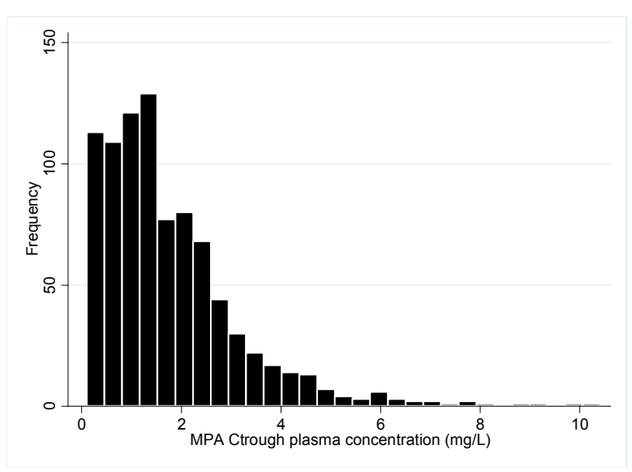
Graph represents mean mycophenolate weight adjusted doses. Median (IQR) patient weight was 74.5 (66.5, 81) kg. Weight was unavailable for 1 male patient. Average weight of adult male patient = 70kg assumed. Statistical analyses performed using two-way analysis of variances (ANOVA). Statistically significant ($p < 0.05$). The ANOVA model appears to be significant (p=0.0000). Calcineurin inhibitor choice appears to significantly affect the average mycophenolate dose used with overall higher doses being used in the ciclosporin group compared to the tacrolimus group. Mycophenolate TDM did not appear to impact MMF dosing even when interacting with CNI choice.

Mycophenolic Acid Plasma Concentrations

Overall mycophenolic acid concentrations were positively skewed therefore; data were presented as median (IQR) (see **Figure 37**). MPA concentrations achieved overall over 12 month period were 1.4 (0.75, 2.52) mg/L. 37%, 51% and 12% of MPA concentrations were subtherapeutic, therapeutic and supratherapeutic respectively (target range 1 to 3.5mg/L) (see **Figure 37A**). More than 50% of MPA concentrations were measured in the first 3 months post-KT (see **Figure 37B**). The first measured MPA concentration was 0.72 (0.29, 1.02) mg/L with a median (IQR) time to first concentration of 2 (1, 3) days post-KT (n=14). This excluded 9 patients that had a dose change prior to first drug concentration or if first drug concentration was > 7 days post-KT. In this early period frequent subtherapeutic concentrations were observed (see **Figure 37C**) with therapeutic concentrations being achieved by 3 months post-KT (1.02 (0.48, 2.2) mg/L). MMF TDM was less frequent in the late period post-transplantation (<25% of MPA concentrations). MPA concentrations demonstrated wide variability throughout the study period, refer to **Figure 37C**.

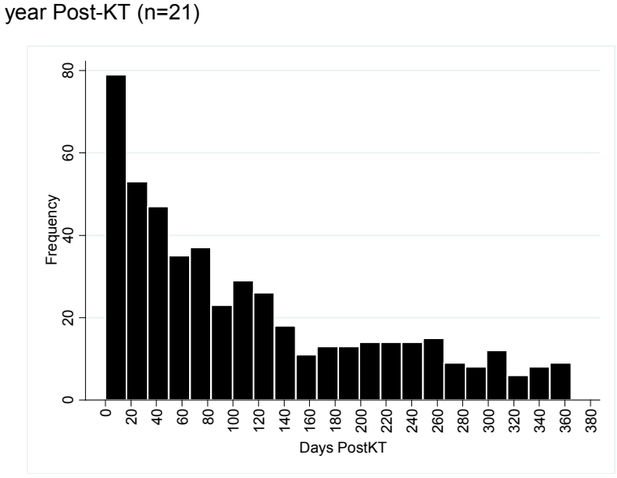
Figure 37: Graph representing overall mycophenolic acid plasma concentrations achieved in the first year post-HIT/KT

A. Histogram of MPA Concentrations in First year Post-KT (n=21)



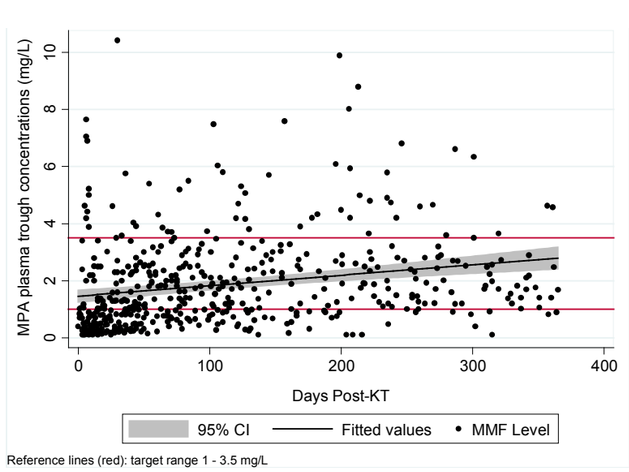
Test for normality based on skewness: Skewness/Kurtosis tests for Normality - Skewness = 1.77, Kurtosis = 7.24, P value = 0.00. Data is positively skewed. P value indicates that it is significantly different from the kurtosis of a normal distribution at the 5% significance level therefore we can reject the hypothesis that MPA concentrations in the first year post-KT were normally distributed.

B. Histogram of the frequency of MPA Concentrations taken in First year Post-KT (n=21)



Test for normality based on skewness: Skewness/Kurtosis tests for Normality - Skewness = 0.86, Kurtosis = 2.63, P value = 0.00. Data is positively skewed. P value indicates that it is significantly different from the kurtosis of a normal distribution at the 5% significance level therefore we can reject the hypothesis that the frequencies of MPA concentrations in the first year post-KT were normally distributed.

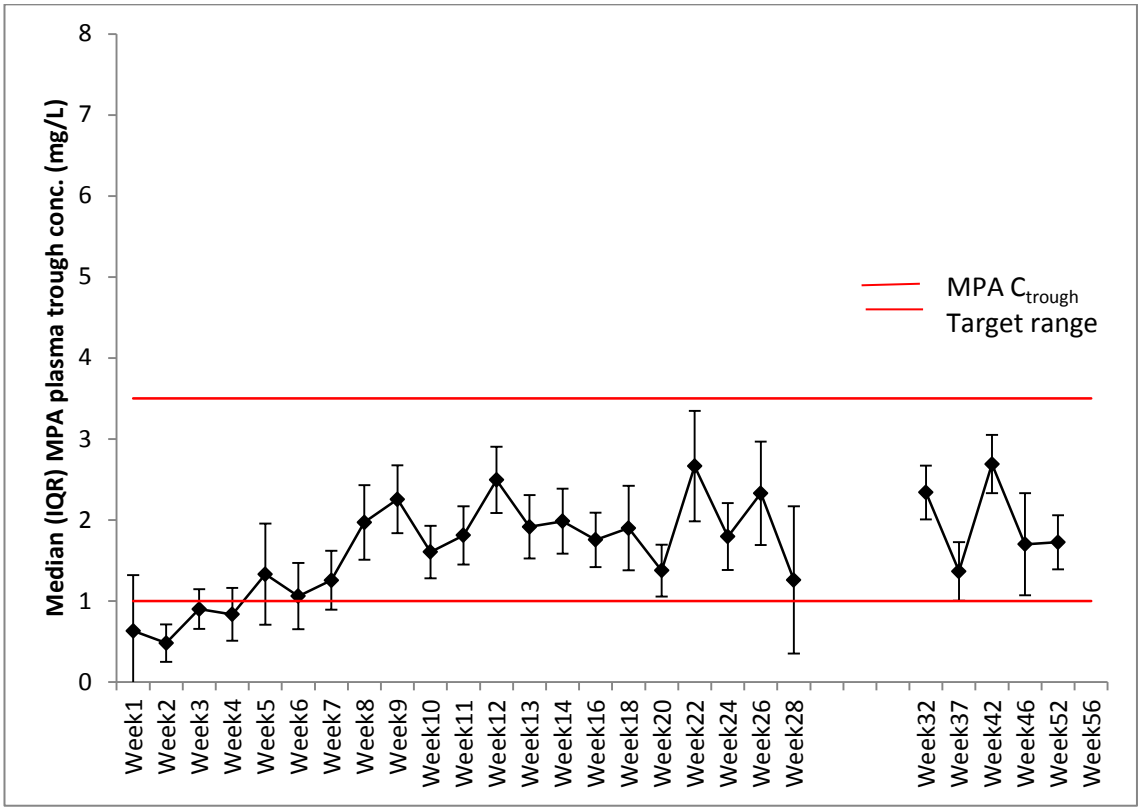
C: Scatter plot of MPA Concentrations in First year Post-KT (n=21)



MPA concentrations in HIV/KT patients in first year post-KT (black circles). The population prediction (solid line) and 95% prediction interval (grey section) are also shown.

For these analyses, each subject contributed a single MPA concentration measurement closest to the time points of interest (i.e weeks 1, 2, 3….) (see **Figure 38**). Therapeutic median MPA concentrations were achieved by week 5 post-transplant and maintained thereafter up to 12 months of follow-up.

Figure 38: Median (IQR) Mycophenolate C_{trough} plasma concentrations categorised by weeks in first year post-KT

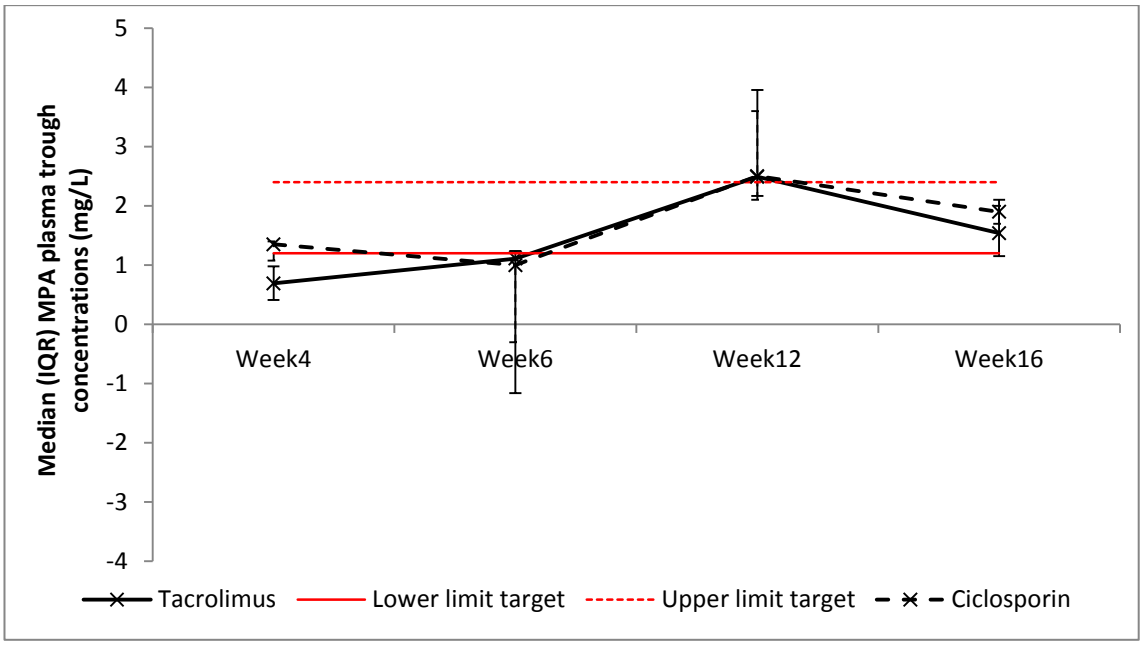


Line graph representing the median (IQR) MPA plasma concentrations. *Concentrations excluded for patients that did not have a concentration measured in the first year post-KT. Where patients had no concentration values on the allocated day of analysis, the last available concentration was carried forward for up to a maximum of 14 days. Concentrations that were carried forward were restricted to period of steady state i.e. excluding week 1.

NB: The half-life of mycophenolate is 12 (normal) - 17.9 (ESRF) hours (Ashely and Currie, 2009). It would therefore take approximately 2 – 4 days to reach steady state (4 to 5 half-lives). However, this does not take into account drug interactions or physiological changes post-KT that may affect mycophenolate disposition.

Within the mycophenolate TDM group only, there was a significantly higher proportion of patients taking tacrolimus (65%, n=15) compared to ciclosporin (35%, n=8) (chi2 p=0.003). An analysis of MPA concentrations in the first four months post-KT stratified by calcineurin inhibitor choice revealed similar concentrations in both CNI groups (see **Figure 39**).

Figure 39: Median (IQR) Mycophenolic Acid Plasma C_{trough} Concentrations Stratified By CNI Choice for the First Four Months Post-HIV/KT

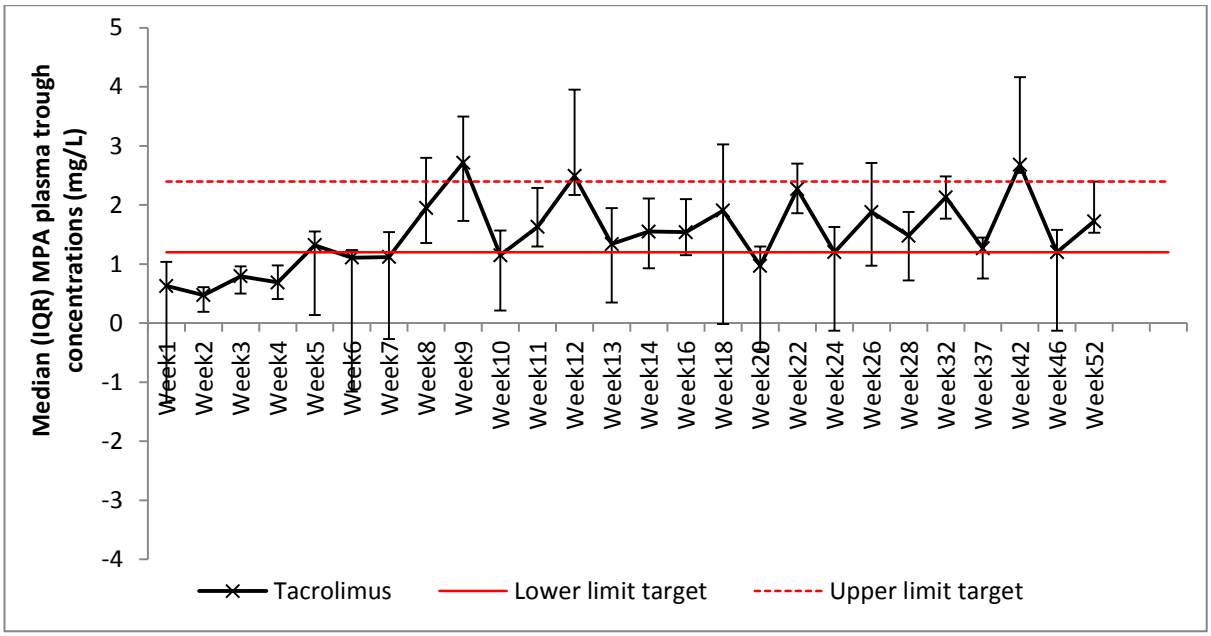


Graph represents median (IQR) MPA plasma trough concentrations stratified by CNI choice. Comparisons for each time point was performed using Wilcoxon rank-sum (Mann-Whitney) test; weeks 4, 6, 12, and 16 p=NS. Statistical significance ($p < 0.05$).

Week	4	6	8	12	16
CsA, n	4	5	2	5	5
Tac, n	9	9	8	7	9
Total, n	13	14	10	12	14

Further comparisons of MPA concentrations between CsA and Tac could not be performed at further times points post-KT (weeks 16 to 52) due to the limited available samples in the ciclosporin group. An analysis of the later period post-KT for the Tac group observed much more stable MPA concentrations maintained within the target range, (see **Figure 40**).

Figure 40: Median (IQR) Mycophenolic Acid Plasma C_{trough} Concentrations for HIV/KT Recipients Maintained on Tacrolimus



WEEK	1	2	3	4	5	6	7	8	9	10	11	12	13
N	12	12	10	9	11	9	9	8	6	10	9	7	6

WEEK	14	16	18	20	22	24	26	28	32	37	42	46	52
N	5	9	10	10	7	9	6	8	10	11	7	9	8

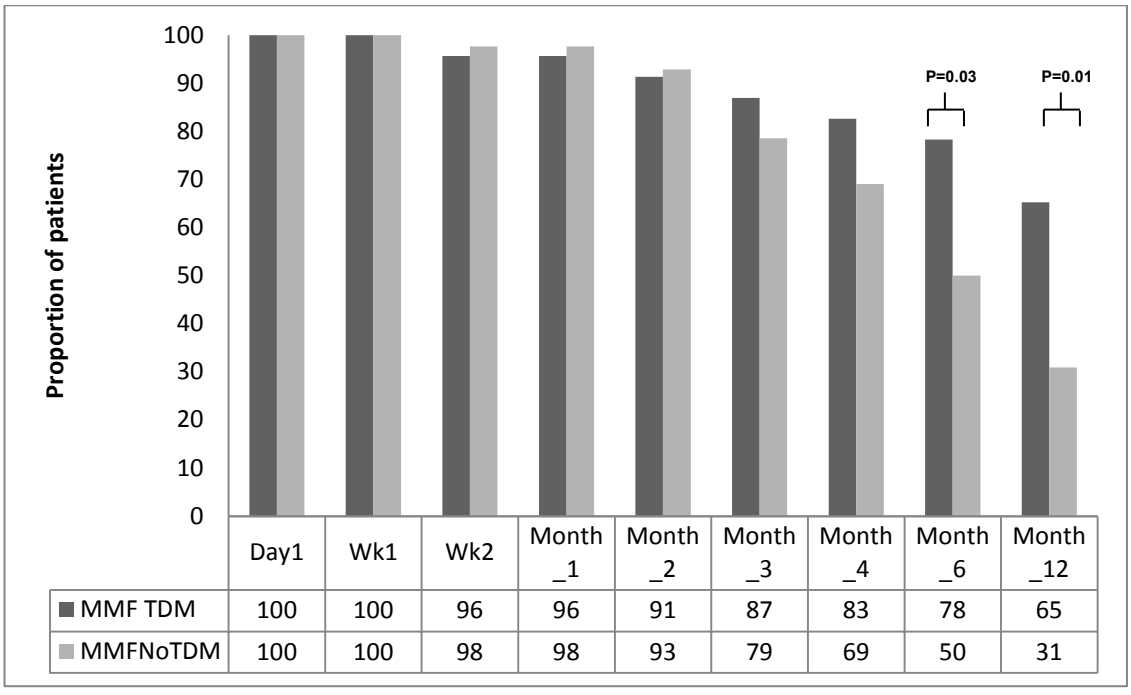
Graph represents median (IQR) mycophenolic plasma concentrations for n=15 HIV/KT recipients being maintained on Tacrolimus IS based therapy in the first year post-KT.

Analyses of MPA concentrations stratified by abacavir containing cART vs abacavir free cART observed no statistical differences (data not shown).

Mycophenolate Discontinuation

Overall, the proportion of patients that first discontinued mycophenolate in the No TDM group compared to the TDM group were similar, 51% (21/42) vs 26% (6/23) respectively, p=0.07. There was a significant difference between groups (MMF TDM vs No TDM) of patients that first discontinued MMF at month 6 and 12 post-KT (see **Figure 41**). There were no statistical differences found in the proportion of first mycophenolate discontinuations that were attributed to latent viral reactivation between TDM groups, 61% (17/28) No TDM vs 17% (1/6) TDM, p=0.08 (see **Table 36**). Cytomegalovirus infection was prevalent in the No TDM group (40%, n=11) compared to the TDM group that had no CMV infection cases. This was also the case for haematological ADR as the reason for first MMF discontinuation, No TDM 25% (7/28) vs. TDM 67% (4/6), p=0.12.

Figure 41: Graph representing the proportion of patients taking mycophenolate in the first year post-HIV/KT stratified *a priori* by TDM status



	Day1	Wk1	Wk2	Month_1	Month_2	Month_3	Month_4	Month_6	Month_12
MMF TDM	100	100	96	96	91	87	83	78	65
MMFNoTDM	100	100	98	98	93	79	69	50	31

* Comparing proportions (%), two-sample test of proportions. All other time points were NS (not shown). Patients were censored at (1) first mycophenolate discontinuation (2) last clinic visit or at 12 months (3) death

Table 36: Reasons for first mycophenolate dose discontinuations stratified by TDM*

	Mycophenolate TDM (n=6) N (%)	Mycophenoate No TDM (n=21)** N (%)	P value
Latent viral reactivation	**1 (17)**	**16 (57)**	0.08
Cytomegalovirus	-	11 (40)	
BK virus	1(17)‡	3 (11)	
Herpes simplex virus	-	3 (11)	
Haematological ADR	**4 (67)**	**7 (33)**	0.12
Low white cell count	3 (50)	3 (11)	
Leukopenia	1 (17)	-	
Neutropenia	-	1 (4)	
Thrombocytopenia	-	2 (7)	
Pancytopenia	-	1 (4)	
Other	**1 (17)**	**4 (19)**	0.91
MMF switched to Azathioprine, pregnancy planning	-	1 (4)	
MMF stopped for acute allograft rejection with ATG	-	2 (7)	
CNI toxicity switched to SrL, MMF stopped to avoid SrL+MMF interaction	1 (17)	1 (4)	

*Table count stated per clinical event; patients with mixed clinical picture contributed multiple times to count, % shown number clinical events represent the denominator. **Missing data on n=1; ‡BK nephropathy; n=2 in TDM group and n=7 in No TDM that did not complete 12 month of follow-up. Statistics: comparison of proportions, ttest (two sample test of proportions) significance <0.05.

Table 37: Reasons for Mycophenolate dose reduction stratified by TDM*

	Mycophenolate TDM (n=5) N (%)	Mycophenolate No TDM (n=13)** N (%)	P value
Latent viral reactivation	**5 (71)**	**10 (67)**	0.85
Cytomegalovirus	3 (43)	9 (60)	
BK virus	1 (14)	1 (7)	
Herpes simplex virus	1 (14)	-	
Haematological ADR	**1 (14)**	**3 (20)**	0.73
Low white cell count	1 (14)	2 (13)	
Leukopenia	-	1 (7)	
Neutropenia	-	-	
Other	**1 (14)**	**2 (13)**	0.95
High MMF C_0 concentration	1 (14)	-	
Low immunoglobulin level	-	1 (7)	
Reduce pill burden	-	1 (7)	

Key: MMF C_0 concentration – mycophenolate trough plasma concentration

*Table count stated per clinical event; patients with mixed clinical picture contributed multiple times to count, % shown number clinical events represent the denominator. **Missing data on n=1

Overall, there was a similar proportion of patients experiencing mycophenolate dose reductions in the first year post-HIV/KT in the No TDM group compared to TDM group, 22% (5/23) vs. 32% (13/41) p=0.39 (**Table 37**). Similarities were also observed for MMF dose reductions attributed to latent viral reactivation in the TDM and No TDM groups, 71% (5/7) vs. 67% (10/15) p=0.85. There were no differences between groups where MMF dose reductions were performed due to haematological ADRs, TDM 14% vs. No TDM 20% p=0.75. In univariate cox-proportional hazard analyses, no factors were found to be associated with first mycophenolate discontinuations **Table 39**. Cox proportional hazard univariable analysis CNI choice was the only factor significantly associated with mycophenolate discontinuation with tacrolimus based IS therapy being protective (hazards ratio (HR) 95CI 0.27 (0.12, 0.65), **Table 38**.

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Table 38: Factors Associated with Mycophenolate Discontinuation in the First Year Post-HIV/KT

	Univariate analysis	
	HR (95CI)	P
Mycophenolate TDM		
Yes	1.00	
No	0.42 (0.17, 1.05)	0.06
Ethnicity		
Black	1.00	
Other	0.92 (0.37, 2.28)	0.85
Gender		
Male	1.00	
Female	(0.66, 0.28)	0.34
Hepatitis B co-infection		
Yes	1.00	
No	0.68 (0.23, 1.95)	0.47
Hepatitis C co-infection		
Yes	1.00	
No	0.94 (0.22, 3.95)	0.93
Recipient CMV IgG		
Positive	1.00	
Negative	0.91 (0.28, 3.01)	0.88
Unknown	1.88 (0.72, 4.92)	0.20
Donor CMV IgG		
Positive	1.00	
Negative	1.59 (0.54, 4.63)	0.40
Unknown	0.62 (0.15, 2.66)	0.53
CMV Prophylaxis		
Yes	1.00	
No	1.21 (0.57, 2.58)	0.62
Allograft type		
Cadaveric	1.00	
Living	1.50 (0.70, 3.25)	0.30
Delayed Graft Function		
Yes	1.00	
No	1.30 (0.52, 3.22)	0.57
cART regimen		
PI-containing	1.00	
PI-sparing	0.92 (0.43, 1.98)	0.82
Abacavir use		
Yes	1.00	
No	0.69 (0.32, 1.47)	0.33
CNI Choice		
Tacrolimus	0.27 (0.12, 0.65)	**0.003**
Ciclosporin	1.00	

Key: HR=Hazard ratio estimated from Cox proportional hazard regression model with 95CI of the estimated HR. CI=Confidence Interval; P=p-value; Analyses censored at first mycophenolate discontinuation, last clinic visit or 12 months. Statistical significance p<0.05.

Mycophenolate Associated Adverse Events

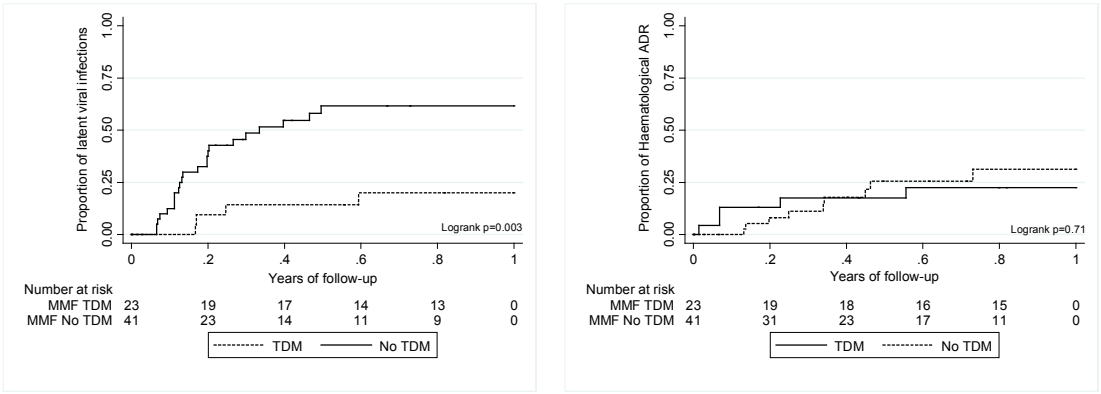
Kaplan Meier analyses showed significant differences in the cumulative incidence of latent viral reactivation at 1 year in the MMF TDM vs No TDM groups was 20% and 62% respectively (p=0.003), (see **Figure 42A**). Although, in the MMF TDM group there was a higher proportion of patients that received CMV prophylaxis compared to the No TDM group, 74% (n=17) vs 43% (n=18), p=0.02. The cumulative incidence of latent viral infections at 1-year when adjusted for CMV prophylaxis for both MMF TDM and No TDM groups was 20% vs 84% respectively, p=0.0001. There was a similar incidence of MMF associated haematological ADRs in both groups 22% and 31% at 1-year, MMF TDM vs No TDM respectively (p=0.71), (see **Figure 42B**).

Multivariate proportional hazards analysis showed that mycophenolate TDM, being on Tac based IS therapy and receiving CMV chemoprophylaxis were protective against post-HIV/KT latent viral infections in the first year (HR 95CI, 0.38 (0.17, 0.85), p=0.018; 0.24 (0.08, 0.75), p=0.015; 0.33 (0.13, 0.83), p=0.018 respectively), (see **Table 39**).

In the group without MMF TDM, 31% (n=13) of patients switched CNI therapy choice at a median (IQR) 3.3 (2.6, 5.5) months post-KT. Of the 13 patients all taking CsA at KT, 12 switched to Tac and 1 to SrL. The clinician reported reason for switching was allograft rejection (n=9), failing graft (n=1), Kaposi Sarcoma (n=1), nausea (n=1) and efficacy (n=1).

Figure 42: Cumulative incidence of Adverse Events (AE) stratified by MMF TDM and by AE type in the first year post-transplantation

A: Latent Infections **B: Haematological ADR**



*Patients were censored at (1) date of latent viral infection or Haem ADR (2) date first stopped MMF or (3) last clinic visit (these included patients that did not have complete 12 month follow-up as described above.

**Latent infection: Latent infection count includes for those that had MMF discontinuation or dose reduction. In No TDM group n=1 had missing data and of the remaining 41 patients, n=23 latent viral infections. Of the 18 patients without latent viral infections, n=6 discontinued MMF and n=3 had < 12months of follow-up. In the TDM group none had missing data and n=4 had latent viral infections. Of the remaining 19 patients, n=5 had discontinued MMF and n=2 had <12 months of follow-up. All other patients' in both groups time of follow-up was calculated to 1 year.

**Haematological ADR: Count includes for those that had MMF discontinuation or dose reduction. In No TDM group n=1 had missing data and of the remaining 41 patients, n=9 had Haem ADRs. Of the 32 patients without Haem ADR, n=14 discontinued MMF and n=7 had < 12months of follow-up. In the TDM group none had missing data and n=5 had Haem ADRs. Of the remaining 18 patients, n=2 had discontinued MMF and n=2 had <12 months of follow-up. All other patients' in both groups time of follow-up was calculated to 1 year.

Mycophenolate TDM and CNI choice were significantly associated with developing latent viral infections in multivariable cox-proportional hazard regression analyses, **Table 39**. There were no factors associated with first occurrence of MMF-associated haematological ADRs in univariate cox proportional hazard regression analyses, **Table 40**.

Table 39: Results from univariate and multivariate cox-proportional hazard analyses to identify factors associated with latent viral infections in the first year post-transplant

	Univariate analysis		Multivariate analyses	
	HR (95CI)	P	HR (95CI)	P
Mycophenolate TDM				
Yes	1.00		1.00	
No	0.22 (0.08, 0.65)	**0.006**	0.24 (0.08, 0.75)	**0.015**
Ethnicity				
Black	1.00			
Other	0.96 (0.39, 2.37)	0.92		
Gender				
Male	1.00			
Female	0.85 (0.37, 1.95)	0.70		
Hepatitis B co-infection				
Yes	1.00			
No	0.73 (0.25, 2.10)	0.55		
Hepatitis C co-infection				
Yes	1.00			
No	0.66 (0.15, 2.78)	0.57		
Recipient CMV IgG				
Positive	1.00			
Negative	1.20 (0.36, 4.01)	0.77		
Unknown	0.55 (0.13, 2.33)	0.42		
Donor CMV IgG				
Positive	1.00			
Negative	0.68 (0.30, 1.56)	0.30		
Unknown	0.25 (0.08, 0.77)	**0.02**		
CMV Prophylaxis				
Yes	1.00		1.00	
No	0.61 (0.28, 1.33)	0.21	0.33 (0.13, 0.83)	**0.018**
Allograft type				
Cadaveric	1.00			
Living	1.24 (0.57, 2.71)	0.59		
Delayed Graft Function				
Yes	1.00			
No	0.74 (0.32, 1.69)	0.47		
cART regimen				
PI-containing	1.00			
PI-sparing	1.37 (0.62, 3.05)	0.44		
Abacavir use				
Yes	0.83 (0.38, 1.79)	0.63		
No	1.00			
CNI Choice				
Tacrolimus	0.26 (0.11, 0.62)	**0.002**	0.38 (0.17, 0.85)	**0.018**
Ciclosporin	1.00		1.00	

Key: HR=Hazard ratio estimated from Cox proportional hazard regression model with 95CI of the estimated HR. CI=Confidence Interval; P=p-value; Analyses censored at first mycophenolate discontinuation, last clinic visit or 12 months. Statistical significance p<0.05.

Table 40: Results from univariate cox-proportional hazard analyses to identify factors associated with treatment limiting cytopenias in the first year post-transplant

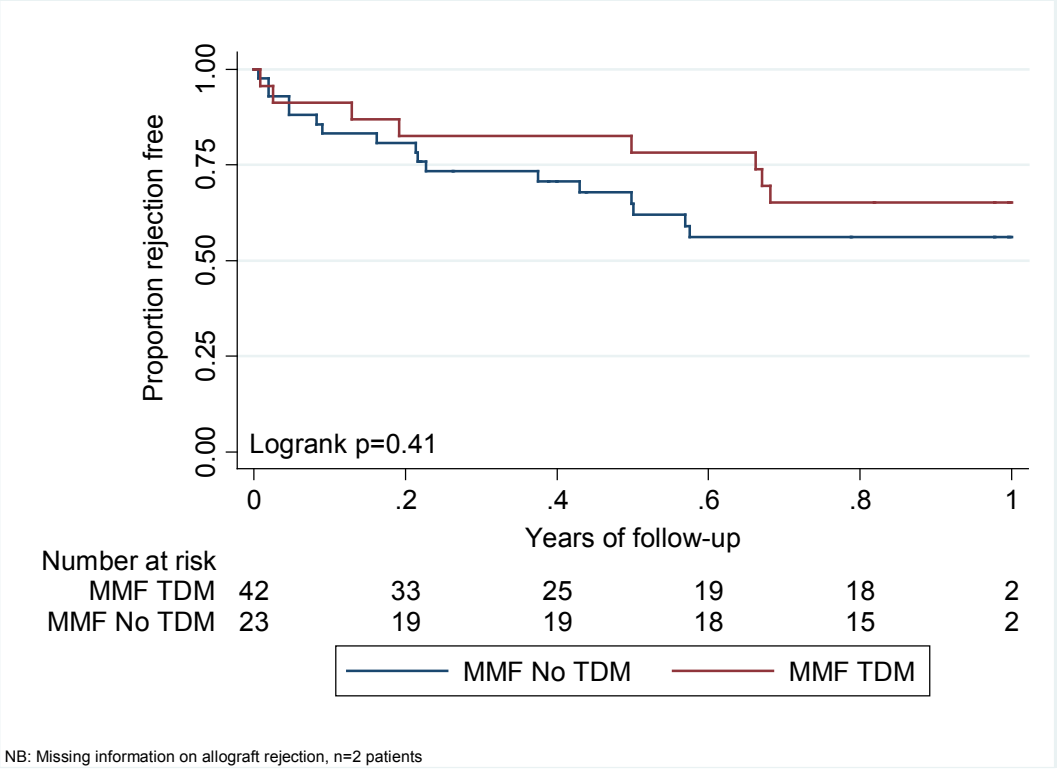
	Univariate analysis	
	HR (95CI)	P
Mycophenolate TDM		
Yes	1.00	
No	0.81 (0.27, 2.44)	0.71
Ethnicity		
Black	1.00	
Other	3.6 (0.48, 27.9)	0.21
Gender		
Male	1.00	
Female	0.47 (0.13, 1.69)	0.25
Hepatitis B co-infection		
Yes	1.00	
No	0.75 (0.17, 3.36)	0.71
Hepatitis C co-infection		
Yes	1.00	
No	1.03 (0.13, 7.89)	0.98
Recipient CMV IgG		
Positive	1.00	
Negative	1.65 (0.36, 7.55)	0.52
Unknown	1.24 (0.27, 5.64)	0.79
Donor CMV IgG		
Positive	1.00	
Negative	0.96 (0.29, 3.15)	0.94
Unknown	0.53 (0.12, 2.21)	0.38
CMV Prophylaxis		
Yes	1.00	
No	1.81 (0.62, 5.24)	0.28
Allograft type		
Cadaveric	1.00	
Living	1.13 (0.38, 3.39)	0.82
Delayed Graft Function		
Yes	1.00	
No	0.61 (0.20, 1.83)	0.38
cART regimen		
PI-containing	1.00	
PI-sparing	0.65 (0.23, 1.84)	0.42
Abacavir use		
Yes	1.00	
No	0.37 (0.12, 1.07)	0.07
CNI Choice		
Tacrolimus	0.79 (0.27, 2.26)	0.66
Ciclosporin	1.00	

Key: HR=Hazard ratio estimated from Cox proportional hazard regression model with 95CI of the estimated HR. CI=Confidence Interval; P=p-value; Analyses censored at first mycophenolate discontinuation, last clinic visit or 12 months. Statistical significance $p<0.05$.

Mycophenolate TDM and Allograft Outcomes

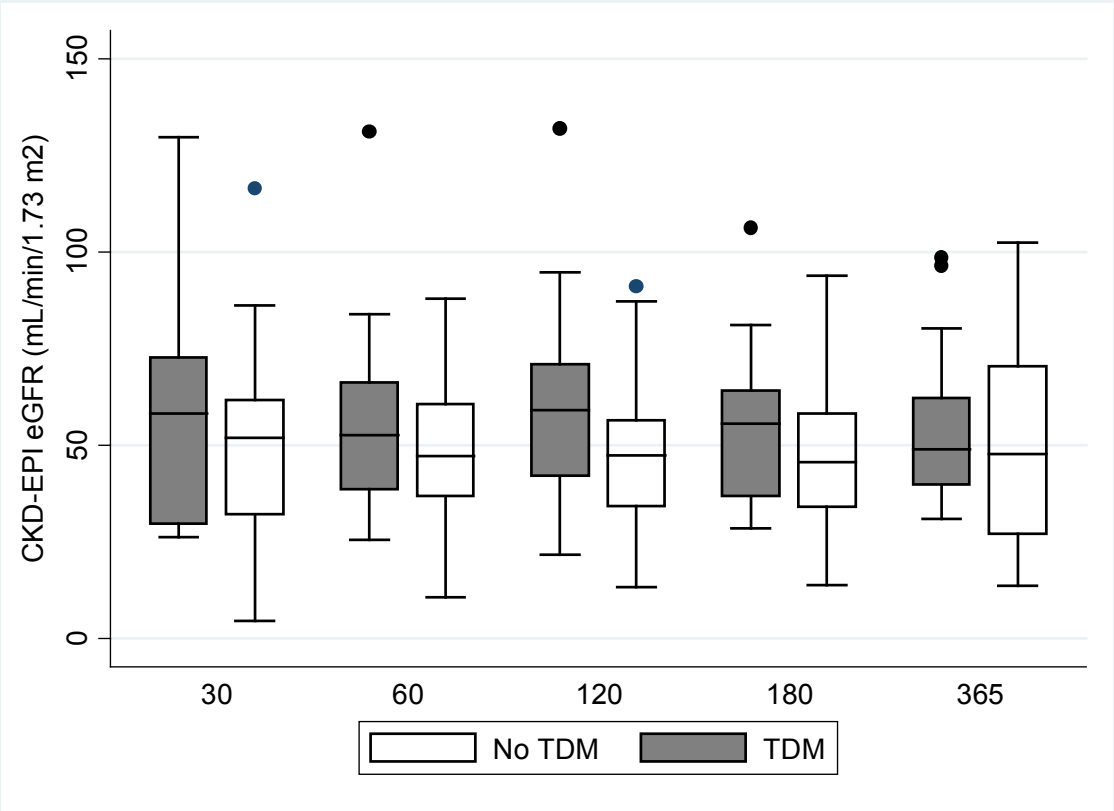
There was no difference in the rates of acute rejection at 1-year observed between groups, (see **Figure 43**). No differences were found in allograft function at the selected time points in those with mycophenolate TDM vs no TDM, (see **Figure 44**). At 1 year, the median (IQR) CKD-EPI eGFR was 48.9 (39.9, 62.3) and 47.7 (27.1, 70.5) mL/min per 1.73 m^2 in the MMF TDM group compared to those without MMF TDM.

Figure 43: First Allograft Rejection Episodes at 1 year Post-HIV/KT Stratified by Mycophenolate TDM



NB: Missing information on allograft rejection, n=2 patients

Figure 44: Graph representing estimated glomerular filtration rate (eGFR) determined by CKD-EPI post-HIV/KT stratified by Mycophenolate TDM



*Ranksum test for all time points P=NS

There were no significant differences in the change of graft function (CKD-EPI eGFR) from baseline to 1 year post-KT when comparing those that had no MMF TDM to those that did (multilevel mixed effect linear regression estimates (95CI) +6.4 (-4.9, +17.7) ml/min/1.73^2, p=0.27). The slope of eGFR over time was also not different between groups (interaction p=0.66). The eGFR seemed to remain stable throughout the follow-up period for both groups (overall change of eGFR MMF No TDM -0.02 (95CI -0.16, +0.10) ml/min/1.73^2, MMF TDM +0.01 (95CI -0.11, 0.13) ml/min/1.73^2).

6.4. Discussion

The need for therapeutic drug monitoring of mycophenolate in clinical practice has been much debated. To date the benefit of mycophenolate TDM has not been demonstrated in HIV kidney transplantation. The current analyses lacked strong evidence to demonstrate the utility of mycophenolate TDM in HIV/KT. First, no association was found between mycophenolate TDM and first MMF discontinuation rates over the initial 12 months post-KT. Second, there was no difference in the occurrence of haematological adverse effects, e.g. treatment limiting cytopenias, in the mycophenolate TDM group compared to the no TDM group. A study of the impact of mycophenolate TDM on allograft outcomes also found no effect on allograft rejection or function. However, despite these findings mycophenolate TDM was protective against developing latent viral infections even after adjusting for CMV prophylaxis in multivariate cox-proportional hazard analyses (HR 95CI, 0.28 (0.10, 0.83), p=0.02). Other secondary findings found being on tacrolimus to be protective against developing latent viral infections (0.32 (0.14, 0.78), p=0.01). However, there was a large proportion of patients in the mycophenolate TDM group taking Tac and on CMV prophylaxis (65%, n=15). Furthermore, these patients were initiated on lower doses as a preemptive dosing strategy to manage the known tacrolimus andmycophenolate drug interaction (Hubner et al., 1999, van Gelder et al., 2000, Miller and Williams, 2009).

Mycophenolate dose and exposure

In recent years, therapeutic drug monitoring to improve mycophenolate therapy outcomes has been reviewed against select criteria. The criteria have included: relationship between MMF exposure and clinical outcomes (e.g. allograft function or rejection); relationship of MMF exposure and immunosuppressive effect; relationship between MMF exposure and toxicity; an adequate measure of efficacy i.e. mycophenolic acid trough or total exposure AUC; and, target therapeutic MPA drug concentrations (Bullingham et al., 1998, Kuypers et al., 2010).

Mycophenolate dosing more recently in clinical practice has been based on fixed dosing 2g/day (Le Meur et al., 2007, van Gelder et al., 2008, Gaston et al., 2009, Grinyo and Cruzado, 2009, Grinyo et al., 2009, Kamar et al., 2009, Kuypers et al., 2010). Where tacrolimus is co-administered, a pre-emptive dose adjustment of 1g/day has been used in anticipation of increased MMF exposure (Kuypers et al., 2003). A similar approach was observed in our study where initiating MMF doses for those taking CsA, Tac respectively were 2 and 1.5 g/day. There is weak evidence that calcineurin inhibitors alter MPA exposure by inhibiting glucuronidation (Kobayashi et al., 2004). The increased MPA exposure noted with ciclosporin is thought to be due to reduced biliary excretion of MPA-glucuronide (Kobayashi et al., 2004). There are some analytical assays commonly used e.g EMIT, are known to be less specific in measuring MPA plasma concentrations (Schutz et al., 1998). The antibody used in the EMIT assay is known to cross-react with one of the glucuronide metabolites, AcMPAG. Therefore, MPA concentrations measured by EMIT tend to overestimated (Jeong and Kaplan, 2007).

In a large randomised clinical study (n=901), initiating fixed MMF doses of 2g/day coincided with total MPA exposure (AUC) of 30 to 60 mg x h/L (van Gelder et al., 2008). Recommended target concentrations of MPA AUC 30 to 60 mg x h/L have demonstrated relationship with good clinical outcomes (i.e. allograft rejection, graft loss, MMF discontinuation) (van Gelder et al., 1999, Le Meur et al., 2007, van Gelder et al., 2008) and reduced MMF toxicity (van Gelder et al., 2006, Kuypers et al., 2008). Target trough MPA concentrations of 1.3 and 1.9 mg/L for Tac, CsA respectively demonstrated best correlation to AUC >30 mg x h/L (van Gelder et al., 2006). MPA AUC < 30 mg x h/L (MPA C_{trough} ≥ 1.3 mg/L) has been demonstrated to correctly identify ~80% patients at risk of early (0 to 3 months) allograft rejection (Kiberd et al., 2004). Study subjects taking CsA based CNI therapy tended to take longer to achieve target MPA concentrations compared to those taking Tac, 51.2% vs 76.2% day 3 post-transplantation respectively (van Gelder et al., 1999). This was also demonstrated in the APOMYGRE study where those taking CsA and 2g/day fixed dose of MMF 73, 69, and 44% achieved MPA AUC (<30mg x h/L) by days 7, 14 and 30 post-transplant (Le Meur et al., 2007). In this study, 25% of overall trough MPA concentrations were ≥ 1.3 mg/L by day 30 post-HIV/KT. During the later period post-KT (6 to 12 months), there was minimal MMF dose change to maintain adequate MPA concentrations. There were no pharmacokinetic studies performed to determine MMF total exposure in this study. Although clinical studies describe standard MMF doses and concentrations achieved, there are other multiple factors that may impact MMF exposure. Mycophenolate exposure can be influenced by multiple factors resulting in wide inter/intra-patient variability. Some of these factors include food, race, severe renal

impairment (GFR <25ml/min), albumin level, delayed graft function, concomitantly administered interacting drugs and polymorphisms of metabolic enzymes and multidrug resistance proteins (Staatz and Tett, 2007, Grinyo et al., 2009).

The absorption of MPA varies with the different mycophenolate formulations. This can result in a delayed enterohepatic recirculation of MPA resulting in higher and variable trough concentrations (Pawinski et al., 2013). Therefore, limited sampling strategies have been developed as better correlates of AUC albeit impractical in clinical settings (Pawinski et al., 2013, Cai et al., 2015, Yao et al., 2015). In this study cohort, mycophenolate exposure was determined by MPA plasma trough concentrations in the MMF TDM group. Overall, therapeutic MPA concentrations were achieved by week 5 post-KT. This delay in achieving therapeutic MPA concentrations has been thought to be due to late gastrointestinal absorption and enterohepatic recirculation of MPA observed in early period post-KT (Staatz and Tett, 2007). The inclusion of antibiotics, that affect enterohepatic recycling, in the perioperative period post-KT may also hinder achieving adequate MPA concentrations (Kuypers et al., 2010). Frequent CNI dosing alterations and changing steroid doses in the early period post-transplant could also be contributing factors (Staatz et al., 2005, Staatz and Tett, 2007, Kuypers et al., 2010). There was more frequent therapeutic drug monitoring in the early period post-KT (>50% in first 3 months). This reflects general clinical practice with close monitoring in the early period post-KT when there is a higher risk of allograft rejection compared to the late period (>6 months) (Kuypers et al., 2010).

Ciclosporin required higher doses of mycophenolate compared to tacrolimus. The influence of CNI choice on mycophenolate exposure has been described in the literature (Hubner et al., 1999, Vidal et al., 2000, Pou et al., 2001, Grinyo et al., 2009, Naito et al., 2009). The co-medication of ciclosporin with MMF results in approximately 30 to 40% lower MPA concentrations compared to tacrolimus (Staatz and Tett, 2007). In this cohort, we anticipated that the inclusion of certain antiretroviral drugs that interact with CNIs may have an added impact on MPA exposure. However, no relationship was found between cART choice (PI-sparing vs PI-containing) and MPA concentrations. There is also the potential for altered MPA concentrations when mycophenolate is co-administered with antiretroviral drugs that undergo glucoronidation e.g. abacavir (UoL, 2015). Close monitoring of mycophenolate concentrations is recommended when be performed with co-administered with abacavir (UoL, 2015). However, alterations to MPA concentrations by abacavir have not been demonstrated in pharmacokinetic studies (Sankatsing SU, 2004, Millan et al., 2005). In this study cohort, no relationship was found between abacavir and trough MPA concentrations.

At baseline patients in both groups in this study were well matched except for the higher proportion of male patients in the MMF no TDM group 76% (n=32) compared to the TDM group, 48% (n=11) (p=0.02). It has been demonstrated that (a) males have more rapid apparent MPA clearance than females (Tornatore et al., 2015) (b) males have higher glucoronidation of MPA than females (Morissette et al., 2001). It has also been suggested that MPA metabolism is reduced in females due as oestrogen competes with MPA for UGT binding (Morissette et al., 2001). However, clinical studies have not proved

gender differences for mycophenolate requirements or exposure (Pescovitz et al., 2003, Le Guellec et al., 2004, Staatz et al., 2005).

At baseline both study groups were well matched for ethnicity, consideration of ethnicity on MMF exposure was given owing to the high proportion of patients of black ethnicity in this study cohort. Some evidence of reduced MMF efficacy has been demonstrated in African Americans compared to Caucasian kidney transplant recipients (Neylan, 1997, Schweitzer et al., 1998, Staatz and Tett, 2007). Although, strong evidence is lacking that show the impact of ethnicity on MPA pharmacokinetics (Shaw et al., 2000, Pescovitz et al., 2003, Staatz and Tett, 2007). In this cohort, there was no relationship found between MPA concentrations and ethnicity ($p=0.06$).

Pharmacogenetic considerations on mycophenolate disposition have been investigated. There are two genes prognostic of acute allograft rejection that have been identified, *UGT1A9* and *IMPDH1* genes. *UGT1A9* genes occur in approximately 15% of Caucasians (Girard et al., 2004). Similarly, *IMPDH1* genes have been commonly reported in Caucasians of European descent (Sombogaard et al., 2009, Wu et al., 2010). Although strong evidence is lacking on the influence of these genotypes on mycophenolate disposition (Abboudi and Macphee, 2012).

Mycophenolate Discontinuation

Mycophenolate discontinuation especially in the first year post-transplant compromises the efficacy of the immunosuppression putting the allograft at risk of rejection. In this study, there was somewhat similar rates of MMF discontinuation between groups no TDM 51% (21/42) vs TDM 26% (6/23) respectively, p=0.07. In multivariate analyses, being on Tac was protective for MMF discontinuation (0.27 (0.12, 0.65), p=0.003). The impact of MMF discontinuation on post-KT outcomes is much debated. Some evidence suggests that early MMF discontinuation (up to 3 months) does not increase the incidence of allograft rejection at 6 months (Pascual et al., 2006, Sulowicz et al., 2007). Whereas other evidence suggests that MMF dose reduction and discontinuation increases the risk of allograft rejection and graft loss (Knoll et al., 2003, Hardinger et al., 2004a, Tierce et al., 2005, Bunnapradist et al., 2006, Machnicki et al., 2008, Opelz and Dohler, 2008, Shah et al., 2008).

Latent viral infection was the most common reason for MMF discontinuation in this study analysis. The cumulative incidence of latent viral infections at 1-year when adjusted for CMV prophylaxis in the MMF no TDM group was almost four times higher than the TDM group. A causal relationship between pharmacokinetic monitoring of MPA and post-transplant infections has not been established. One study describes an increase in the incidence of infections has been found with trough MPA concentrations >3mg/L (Borrows et al., 2006). By contrast, an MPA AUC >60mg x h/L was associated with high risk of haematological ADRs but not infections, specifically viral infections (Satoh et al., 2005, Kuypers et al., 2008). Antiretroviral therapy has dramatically reduced the incidence of opportunistic infections. Although, HIV infected individuals with

CD4 T cell count < 100 cells/mm^3, when reconstitution of normal immune responses do not occur, have an increased risk of latent viral reactivation and recurrence of disease (Springer and Weinberg, 2004). Furthermore, there is risk of end-organ disease with latent viral reactivation -e.g. CMV (Spector et al., 1996, Springer and Weinberg, 2004). Some authors argue that this warrants preemptive CMV prophylaxis in HIV infection (Paltiel et al., 2001). Our data suggests that in the transplant setting, that irrespective of preemptive CMV prophylaxis MMF TDM may be beneficial in preventing latent viral infection. However, this association needs to be corroborated in a larger cohort. A post-hoc analysis of CD4 T cell counts revealed counts were > 350 cells/mm^3 in both MMF TDM and no TDM groups throughout the study period (data not shown).

Mycophenolate TDM & Allograft Outcomes

Overall, there were no differences in allograft rejection rates or graft function observed between MMF TDM and No TDM groups. In the general KT population, there is conflicting evidence of the impact of mycophenolate TDM on allograft rejection. In a clinical study that included 549 patients considered 'high risk', a difference in the incidence of AR was observed in those that achieved MPA AUC > vs < 30 mg hr/L respectively, 14.3% vs 7.8% (p=0.025) during the first month post-KT (van Gelder et al., 2010). By contrast, the Opticept study (n=720) intention to treat analysis did not find an association of MMF TDM to allograft rejection (Gaston et al., 2009). Although, a *post-hoc* analysis of the Opticept study demonstrated a significant relationship in KT recipients taking tacrolimus (n=590) between BPAR and MPA trough concentrations <1.6mg/L (p=0.001).

The impact of mycophenolate TDM on post-transplant allograft function has been explored. One clinical study including 46 HIV negative kidney transplant recipients found trough MPA concentrations to be significantly correlated with creatinine clearance (Cattaneo et al., 2001). The study demonstrated that an MPA $AUC_{0\text{-}12}$ > 40 µg/mL·h had better allograft function (85.7 mL/min) compared to < 40 µg/mL·h (64.5 mL/min) (Cattaneo et al., 2001).

Study Limitations

The strength of this study is the well matched groups at baseline except for gender. However, the study had several limitations which may have affected inferences drawn. Firstly, analyses when assessing the sub-groups were limited by the small cohort size. Secondly, in the MMF TDM group variability in immunoassays both within and between centres could not be controlled due to the small sample size and lack of detailed information on assay modifications thoughout the study period. Also, the differences in immunoassay accuracy, e.g. those that measure both MPA and MPAG, is questionable. For these reasons, target MPA trough concentrationscan be variable. Further, the lack of evidence to establish the relationship of C_{trough} and AUC, may have limited the inferences drawn from this study. The use of clinician reported data, e.g. treatment limiting cytopenias, meant that analyses could not be standardised thereby reducing bias. In addition, the variation in transplant protocols also meant that post-transplant management was inconsistent e.g. steroid withdrawal, empirical MMF dose reductions, use of pre-emptive chemoprophylaxis.

6.5. Conclusion

There has been much debate over the utility of mycophenolate therapeutic drug monitoring in solid organ transplantation. HIV infected patients are considered to be of high immunological risk of allograft rejection. This study failed to provide strong evidence of the usefulness of MMF TDM in HIV/KT. The composite outcomes that did not support MMF TDM included: MMF discontinuation; mycophenolate associated haematological ADR; and post-transplant allograft outcomes (allograft rejection and function). There was some benefit observed of mycophenolate TDM in the prevention of latent viral infections. The use of CMV prophylaxis and tacrolimus based IS therapy also appeared to be protective for the development of latent viral infections although, these findings need to be corroborated in a larger cohort.

Chapter 7. Conclusions & Future Work

End-stage kidney disease is an important co-morbidity in HIV infected individuals. Management of ESKD in the pre-HAART era was restricted to conservative and dialysis treatment modalities. Both methods were associated with high rates of mortality. During this period, prior to the advent of effective antiretroviral therapy, concerns of developing opportunistic infections, HIV disease progression and poor patient survival were deterrents to kidney transplantation in HIV infected individuals. The prognosis of HIV infection was vastly improved with the use of HAART. Effective management of HIV and use of stringent selection criteria paved the way for the successful kidney transplantation of HIV infected individuals. With low patient numbers for both HIV/ESKD and kidney transplant recipients, observational cohort studies are the best way to glean insights that may help optimise care for these patients.

This thesis was set out to first examine the trends of ESKD in HIV infection in the United Kingdom and to describe the use of and barriers to kidney transplantation as a treatment modality for ESKD. The first study also sought to compare the patient survival outcomes by treatment modality for ESKD. To further prove the feasibility of HIV kidney transplantation, an in depth analysis was performed to describe the host and graft outcomes. Finally with the complexity of kidney transplantation, this thesis explores the immunosuppressive drug therapy management in this HIV/KT cohort.

Trends of ESKD in HIV Infection

The burden of ESKD in HIV infection in the United Kingdom has continued to increase over the past decade. The incidence of HIV/ESKD on the otherhand remained unchanged. This may be reflective of an ageing HIV population and the chronic use of antiretroviral drugs that may contribute to the development of ESKD. Over a 13 year study period there was a 20-fold increase in HIV/ESKD despite the extensive use of antiretroviral therapy. Patients of black ethnicity had a 7 fold higher overall prevalence of ESKD compared to other ethnicities. The high prevalence of APOL-1 gene among patients of black ethnic patients has been implicated for the differences in ESKD rates (Behar et al., 2011, Atta et al., 2012, Allison, 2015, Anyaegbu et al., 2015). Aside from ethnicity, other patient characteristics of HIV/ESKD included longer time since diagnosis, having a high HIV viral load and hepatitis B/C co-infection. This highlights the need for earlier HIV diagnosis and earlier initiation of cART both associated with lower risk of developing ESKD (Allison, 2009). Other factors that were associated with developing ESKD included older age, prior history of AIDS (CDC-C) defining illness, a lower nadir and overall CD4 T cell count. HIV associated nephropathy continued to be the primary diagnosis of ESKD probably owing to the continued proportion of HIV infected patients that present with advanced HIV disease (Scourfield et al., 2011, HPA, 2014). Earlier, more robust and closer monitoring of renal function of HIV infected individuals maintained on cART may be one approach to reducing the rates of ESKD in this population. Current BHIVA guidelines (BHIVA et al., 2014) recommend eGFR in addition to urinalysis to detect haematuria, proteinuria or glycosuria; as a more accurate measure of renal function compared to serum creatinine. Urinary protein monitored by measuring urinary protein/creatinine ratio (uPCR) is also

recommended especially in patients taking nephrotoxic antiretroviral therapy e.g. tenofovir.

At the end of the study, those that were eligible for KT had received an allograft. Poor HIV virological control was the primary reason that prevented the HIV infected individuals from receiving an allograft. Public health intiatives are necessary for earlier HIV diagnosis and ealier cART initiation. Furthermore, the utilisation of adherence clinics to improve behavioural outcomes and virological responses are warranted (Rathbun et al., 2005, Horne et al., 2007, Cooper et al., 2011, Charania et al., 2014, Muessig et al., 2015). One prospective, randomised, controlled study demonstrated this in a pharmacist led adherence clinic approach where there was improved adherence, 69% vs 42% (p=0.025); and HIV RNA levels declined to <400 copies/mL by week 16 for 100% vs 71%, p=0.04 of the adherent group compared to the control group respectively (Rathbun et al., 2005). A comparison of patient survival between dialysis and KT treatment modalities for HIV/ESKD patients revealed similar five year survival rates. Despite demonstrating that KT offers a survival benefit, other benefits of KT not measured in the current analysis e.g. quality of life measures, cardiovascular co-morbidities and health economics warrant further study.

HIV kidney transplantation

This thesis confirms the feasibility of kidney transplantation in a select group of HIV infected individuals with well controlled HIV who are stable on antiretroviral drug therapy. Favourable outcomes in terms of patient and graft survival in the short term were observed. Longer follow-up is needed to determine the impact of the high rate of allograft complications on longterm allograft function and survival. There are different approaches for consideration in the HIV/KT population to reduce the rejection rates. Firstly consideration for the quality of donor organs although not measured in the current study. In the current dataset, living donors demonstrated better outcomes compared to deceased donor HIV kidney transplantation. However, for deceased donation donor age, cold ischaemic time and panel reactive antibodies are factors that are implicated in allograft outcomes such as delayed graft function and allograft rejection. Although, organ shortage can be problematic in this group that have a high proportion of ethnic minority patients (NHSBT, 2013). Other ways to combat this may be use of HIV positive organ donors (Muller et al., 2015) or exploring ABO incompatible transplantation (Campara et al., 2008) although, both approaches are not without risks. HIV positive organ donation is a relatively new field and risk of HIV superinfection with a new or perhaps resistant strain is possible. There is also risk of developing kidney disease in the donor for living donation (Muller et al., 2015). Although even with both of these new approaches, allograft rejection continues to be a challenge in the HIV+ cohort. Optimal post-transplant immunosuppressive management is key to overcoming this issue. To start with, the question of which inductive therapy is most effective in the HIV/KT cohort could not be addressed in the present dataset. Use of monoclonal or polyclonal lymphocyte depleting agents in the

general KT patients have proved promising with much allograft rejection rates as low as 7% at 1 year post-KT (Sageshima et al., 2011, 3C.StudyCollaborativeGroup et al., 2014). Although, there has been much debate over the use of these agents in the HIV+ population due to the risks of developing opportunistic infections or serious infections requiring hospitilisation (Carter et al., 2006, Stock et al., 2010a) There has been some recent data to demonstrate that use of polyclonal lymphocyte depleting agents were not associated with an increase in post-HIV/KT infections (Kucirka, 2015). What was encouraging in the current cohort, there was no evidence of HIV disease progression in terms of loss of virological control and/or occurrence of AIDS defining illnesses. Futhermore, there were few opportunistic infections, tumors/neoplasm. However, the lack of serial virology data and protocol cytology reports limited findings. Opportunistic infections were dependent on clinician reporting and definition of OIs was not standardised across study centres. In the USA HIV/KT cohort, patients who were closely monitored for HPV-related anal neoplasia were found to be at a high risk of developing high grade squamous intraepithelial lesions (Nissen et al., 2012). For future study, protocol cervical and anal cytologies should be reviewed for any changes post-HIV/KT.

Another consideration is the choice of calcineurin inhibitor. Findings demonstrated that choice of calcineurin inhibitor was significantly associated with allograft rejection. Results demonstrated that use of tacrolimus was associated with a lower allograft rejection rate compared to ciclosporin based immunosuppression drug therapy. This suggests that that tacrolimus would be the preferred choice for the management of HIV kidney transplant recipients. This finding is consistent with data from the general KT population (Pirsch et al.,

1997, Ferraris et al., 2004, Abou-Jaoude et al., 2005, Boratynska et al., 2006)- and other published HIV/KT cohorts (Stock et al., 2010b, Touzot et al., 2010). Despite CNIs being effective for KT management, there are concerns of CNI toxicity where CNI minimisation, CNI free regimens offer for attractive alternative strategies (Sawinski et al., 2016). The use of mTOR inhibitors in combination with low dose CNIs has been studied in the HIV negative KT population. Improved graft function and reduced CNI nephrotoxicity with low dose CNI are some the benefits that have been demonstrated in RCTs (Nashan et al., 2004, Salvadori et al., 2009, Langer et al., 2012, Bechstein et al., 2013, Oh et al., 2015). mTOR inhibitors have some benefit to suppressing HIV-1 infection through by down regulating C-C chemokine receptor type 5 (CCR5) receptor responsible for HIV entry into CD4+ T cells (Gilliam et al., 2007, Heredia et al., 2008, Nicoletti et al., 2009, Donia et al., 2010). In the USA study cohort, the use of sirolimus, an mTOR inhibitor, was found to have the most significant effect in reducing HIV persistence compared to calcineurin inhibitor drugs, tacrolimus and ciclosporin (Stock et al., 2014).However, the use of mTOR inihibitors without CNIs does not have strong evidence of clinical efficacy in kidney transplantation (Yang and Wang, 2015).

CNI toxicity could not be proven in the current dataset; this was probably due to the infrequent protocol biopsies (Krejci et al., 2010, Sharma et al., 2010). One protocol biopsy study in a HIV negative KT recipient cohort (n=158) of the toxic changes observed 52% were subclinical (Krejci et al., 2010). It has been suggested that surveillance or protocol biopsies are unnecessary due to their associated safety risks but there is some evidence for their utility in high risk patients (Wilkinson, 2006).

Calcineurin inhibitor and Antiretroviral drug interactions

Aside from CNI choice, altered CNI exposure resulting from the co-administration of interacting antiretroviral drugs could have been further implicated in AR development in our cohort. However, as this was an observational study robust analysis to demonstrate the relationship between CNI exposure and AR could not be performed. Despite this, analyses in this thesis described the challenges of achieving and maintaining therapeutic CNI C_{trough} in clinical practice over the first year post-transplant in HIV kidney transplant recipients. The co-administration of antiretroviral drugs with calcineurin inhibitors resulted in unpredictable drug exposure. Frequent subtherapeutic C_{trough} concentrations were observed in the early period post-transplantation. This may have contributed to the high allograft rejection episodes observed although, would require further study to support this inference. Perhaps the availability of non-interacting antiretroviral agents such as raltegravir, dolutegravir and rilpivirine offer for alternatives to allow for the more widespread use of tacrolimus in the HIV infected population. Where switching to integrase inhibitors is not possible, there are several points to consider when co-medicating CNIs with interacting cART, especially for tacrolimus and PI-containing cART combinations.

PI-containing cART profoundly increases Tac exposure by more than 100 fold. The implications of this result in

1. Extended dosing interval
2. Altered total drug exposure
3. Extended time to steadystate drug concentration

This poses several issues, first how to initiate tacrolimus in the immediate period post-KT. The BHIVA (2005) guidelines recommended performing a pre-transplant CNI trial as a dose finding strategy to use post-KT. The utility of this approach could not be proven in the current dataset nevertheless, this approach has several limitations. As discussed, differences in haemodynamics pre- and post-KT of the HIV+ patient that may affect total exposure of the drug; and use of medication peri-operatively that may affect tacrolimus absorption for example. Therefore, Tac initiation using the pre-KT dose finding trial may not be a useful strategy. The second issue with Tac initiation is the extended time to steadystate of Tac concentration and altered total drug exposure. The use of a loading dose either using a standardised single dose, e.g. 1mg or 2mg as previously mentioned, or reducing the dosing interval, e.g. 0.5 three times a week, reducing to two times a week then once a week thereafter may be another approach to achieve a target therapeutic C_{max} and quicker time to steadystate. However, this approach is dependent on the Tac-PI interactions resulting in linear kinetics of tacrolimus (Burton, 2006). The linearity of the Tac kinetics when co-medicated with ritonavir based cART has been implied in a small PK study the tested different ranges of Tac (1mg to 6.5mg) (van Maarseveen et al., 2013). There is also the possibility of using smaller doses more frequently (e.g. 0.2mg daily, two or three times a week) by using liquid formulations of Tac that may offer more rapid absorption for a higher C_{max}, minimise fluctuatioins (C_{max}/C_{min}) in CNI exposure and longer T_{max} compared to immediate release capsule formulations(Burton, 2006, AstellasPharma, 2015). However, further study in a larger cohort is warranted to corroborate these approaches. For all other CNI and cART group combinations, doses described in this thesis could be used as a guide to initiating CNI doses post-KT.

Mycophenolate TDM

Mycophenolate use is known to increase the risk of latent viral reactivation and other associated adverse events. Discontinuing mycophenolate would compromise optimal IS therapy. There has been much debate over the utility of mycophenolate therapeutic drug monitoring in solid organ transplantation. Analyses did not provide strong evidence to support the usefulness of mycophenolate TDM in HIV/KT determined by composite outcomes MMF discontinuation, MMF associated haematological ADR and post-transplant allograft outcomes. However, there was some evidence to support the use of MMF TDM in preventing latent viral infections even with CMV prophylaxis being taking into consideration. However, findings were limited by the small cohort size particularly when performing sub-group analyses. Future studies in a larger cohort is needed.

In conclusion, this programme of research has demonstrated the increasing problem of ESKD in HIV infected individuals, especially in Black ethnic patients, despite the widespread use of cART. Kidney transplantation in HIV infected individuals is feasible albeit with a high rate of allograft rejection. However, optimal immunosuppressant drug treatment strategies are warranted to improve post-HIV/KT outcomes. CNI choice, achieving and maintaining therapeutic CNI C_{trough} concentrations especially in the early period post-KT and utilising mycophenolate therapeutic drug monitoring are but some of the ways to optimise IS therapy and avoid allograft rejection. Other strategies such as use of lymphocyte depleting agents, for example alemtuzumab (anti-CD52 monoclonal antibodies), have shown early promising results although further study in a larger patient cohort would firm up these observations.

Future studies

This thesis has been able to address several questions in relation to kidney transplantation in the HIV infected population. Despite this, several research questions have been raised for future study summarised but not limited to the following

- Study of the impact of antiretroviral drug choice on the incidence/prevalence of HIV/ESKD
- Study of the impact of adherence clinic to improve the uptake of kidney transplantation in HIV infected patients
- Study of impact of HIV/ESKD treatment modality on the patients' quality of life
- Imact of HIV kidney transplantation on host/graft survival at 5 and 10 years post-transplant and implications of allograft rejection on long-term outcomes
- Study to determine the optimal donor criteria to improve HIV kidney transplant allograft outcomes. A background to this is would be to perform a paired controlled study to determine the outcome of the second kidney for the deceased donor HIV/KT patients.
- Utility, safety and efficacy of lymphocyte depleting agents e.g. alemtuzumab and antithymocyte globulin to reduce the rates of allograft rejection in the HIV/KT cohort
- Surveillance protocol biopsies with additional histopathology studies to determine HIV deposits in podocytes or tubular cells (Canaud et al., 2014)
- Use of CNI minimisation and CNI-sparing immunosuppressive therapies to minimise CNI exposure and avoid nephrotoxicity. Study to explore the inclusion of mTOR inhibitors that has demonstrated anti-HIV activity and reduced HIV persistence post-HIV/KT (Stock et al., 2014)
- Study of the safety and efficacy of switching to integrase inhibitors to avoid CNI and PI-containing cART interactions
- Study of the safety and efficacy of HIV positive organ donation
- Study of the safety and efficacy of ABO incompatible transplantation

Appendix A

Publications and Conference Presentations

Publications

End-stage kidney disease and kidney transplantation in HIV-positive patients: an observational cohort study. (Chapter 2)

Gathogo E, Jose S, Jones R, Levy JB, Mackie NE, Booth J, Connolly J, Johnson M, Leen C, Williams D, Sabin CA, Post FA. J Acquir Immune Defic Syndr. 2014 Oct 1;67(2):177-80.

Kidney transplantation in HIV positive adults: the UK experience. (Chapter 3)

Gathogo E, Hamzah L, Hilton R, Marshall N, Ashley C, Harber M, Levy JB, Jones R, Boffito M, Khoo SK, Drage M, Bhagani S, Post FA, for the UK HIV/Kidney Transplantation Study Group**.** Int J STD AIDS. 2014 Jan;25(1):57-66.

Impact of Tacrolimus Compared With Cyclosporin on the Incidence of Acute Allograft Rejection in Human Immunodeficiency Virus–Positive Kidney Transplant Recipients. (Chapter 4)

Gathogo, Esther MPharm, MSc; Harber, Mark MBBS, PhD; Bhagani, Sanjay FRCP; Levy, Jeremy FRCP; Jones, Rachael BSc, MBBS, MRCP; Hilton, Rachel MA, PhD, FRCP, FRCPE; Davies, Graham BPharm, MSc, PhD; Post, Frank A PhD, FRCP; UK HIV Kidney Transplantation Study Group. Transplantation April 2016 -100(4):871–878.

Conference Presentations

Chapter 2

Gathogo E, Jose S, Jones R, Levy JB, Mackie NE, Booth J, Connolly J, Johnson M, Leen C, Williams D, Sabin CA, Post FA. **End-Stage Kidney Disease and Kidney Transplantation in HIV Positive Patients**, poster presentation at CROI 2014, which was held at the Hynes Convention Center, in Boston, Massachusetts, USA, from March 3, through March 6, 2014.

Jose S, Gathogo E, Jones R, Levy JB, Mackie NE, Booth J, Connolly J, Johnson M, Leen C, Williams D, Sabin CA, Post FA. **End-Stage Kidney Disease and Kidney Transplantation in HIV Positive Patients**, oral presentation at 3rd Joint Conference of BHIVA & BASHH 2014, which was held at the Arena & Convention Center, Liverpool, UK, from April 1, through April 4, 2014.

Chapter 3

Gathogo E, Hamzah L, Hilton R, Marshall N, Ashley C, Harber M, Levy JB, Jones R, Boffito M, Khoo SK, Drage M, Bhagani S, Post FA**. Outcomes of kidney transplantation in HIV-positive patients: the UK experience.** Poster Presentation February 2013, Spring Meeting for Clinical Scientists in Training. Abstracts Published in the Lancet special issue [The Lancet, Volume 381, Page S43, 27 February 2013]

Gathogo E, Hamzah L, Campbell L, Nathan B, Marshall N, Ashley C, Taha H, Mackie N, Dobbie H, Jones R, Levy J, Lawton M, Black H, Fox R, Devaney A, Pinnington H, Sweeney J, Swaden L, Hilton R, Harber M, Bhagani S and Post F for the UK HIV/Renal Transplant Study Group. **The United Kingdom Experience of Kidney Transplantation in HIV-positive Patients.** Poster Exhibition for 6th International AIDS Society Conference on HIV pathogenesis, Treatment and Prevention, 17-20 July 2011

Gathogo E, Hamzah L, Nathan B, Campbell L, Levy J, Jones R, Hilton R, Mackie N, Waldron S, Harber M, Marshall N, Ashley C, Swaden L, Post F, Bhagani S, on behalf of the UK HIV-Kidney transplant study group. **Kidney Transplantation in HIV Infected Patients: The United Kingdom Experience.** Poster Exhibition for 17th Annual British HIV Association Conference Bournemouth, April 2011. Published in the HIV Medicine Journal (Peer-reviewed Journal) April 2011, Volume 12, Issue Supplement s1, Pg 46-47

Invited speaker for CPD Session - The United Kingdom Experience of HIV Kidney Transplantation. British Renal Society conference Manchester, May 2012

Chapter 4

Gathogo E, Harber M, Bhagani S, Levy J, Jones R, Hilton R, Davies G, Post FA on behalf of the UK HIV Kidney Transplantation Study Group. **Risk Factors for Acute Allograft Rejection in HIV Positive Kidney Transplant Recipients,** Oral Presentation at BHIVA 2015 Conference, Brighton, UK

Gathogo E, Harber M, Bhagani S, Baxter J, Lee V, Levy J, Jones R, Hilton R, Davies G, Post FA on behalf of the UK HIV Kidney Transplantation Study Group. **Risk Factors for Acute Allograft Rejection in HIV Positive Kidney Transplant Recipients**, poster presentation at CROI 2015, Washington, USA

Chapter 5

E. Gathogo, L. Hamzah, N. Marshall, L Swaden, C. Ashley, H Black, J. Levy, R. Betmouni, M. Boffito, A Devaney, H Pinnington, R. Hilton, L. Galloway, T. Sadiq, I. MacPhee, S. Khoo, M. Harber, S. Bhagani and F. Post for the UK HIV/Renal Transplant Study Group. **Interactions between combination Anti-Retroviral Therapy (cART) and Calcineurin-Inhibitors (CNI) in HIV/Kidney Transplantation: The United Kingdom Experience.** Poster Presentation at 2011 Annual Conference at the The UK Renal Pharmacy Group "Renal Pharmacy – Another step forward" 23rd & 24th September 2011

Appendix B

UK Collaborative HIV Cohort (UK CHIC) Study Group

The UK CHIC/ESKD study group

Sanjay Bhagani, John Booth, Lucy Campbell, David Chadwick, John Connolly, Esther Gathogo, Lisa Hamzah, Mark Harber, Bruce Hendry, Margaret Johnson, Rachael Jones, Sophie Jose, Ed Kingdon, Emil Kumar, Clifford Leen, Jeremy Levy, Nicola Mackie, Fabiola Martin, Steve McAdoo, Sheila Morris, Frank Post, Michael Rayment, Caroline Sabin, Debbie Williams, Ian Williams

The UK CHIC Steering Committee

Jonathan Ainsworth, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard (Chair), Richard Gilson, Phillip Hay, Mark Gompels, Teresa Hill, Margaret Johnson, Sophie Jose, Stephen Kegg, Clifford Leen, Nicky Mackie, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Caroline Sabin, Memory Sachikonye, Achim Schwenk, John Walsh.

Central Co-ordination

UCL Medical School, London (Teresa Hill, Sophie Jose, Andrew Phillips, Caroline Sabin, Alicia Thornton, Susie Huntington); *Medical Research Council Clinical Trials Unit (MRC CTU), London* (David Dunn, Adam Glabay).

Participating Centres

Barts and The London NHS Trust, London (Chloe Orkin, Nigel Garrett, Janet Lynch, James Hand, Carl de Souza); *Brighton and Sussex University Hospitals NHS Trust* (Martin Fisher, Nicky Perry, Stuart Tilbury, Elaney Youssef, Duncan Churchill); *Chelsea and Westminster Hospital NHS Foundation Trust, London* (Brian Gazzard, Mark Nelson, Matthew Waxman, David Asboe, Sundhiya Mandalia); *Public Health England, London (PHE)* (Valerie Delpech); *Homerton University Hospital NHS Trust, London* (Jane Anderson, Sajid Munshi, Damilola Awosika); *King's College Hospital NHS Foundation Trust, London* (Frank Post, Hardik Korat, Chris Taylor, Zachary Gleisner, Fowzia Ibrahim, Lucy Campbell); *Medical Research Council Clinical Trials Unit (MRC CTU), London* (Abdel Babiker, David Dunn, Adam Glabay); *Middlesbrough, South Tees Hospitals NHS Foundation Trust*, (David Chadwick, Kirsty Baillie, Emma Cope, Marie Gibney, Jane Gibson); *Mortimer Market Centre, University College London* (Richard Gilson, Nataliya Brima, Ian Williams); *North Middlesex University Hospital NHS Trust, London* (Jonathan Ainsworth, Achim Schwenk, Sheila Miller, Chris Wood); *Royal Free Hampstead NHS Trust* (Margaret Johnson, Mike Youle, Fiona Lampe, Colette Smith, Helen Grabowska, Clinton Chaloner, Andrew Phillips); *Imperial College Healthcare NHS Trust, London* (John Walsh, Nicky Mackie, Alan Winston, Jonathan Weber, Farhan Ramzan, Mark Carder); *The Lothian University Hospitals NHS Trust, Edinburgh* (Clifford Leen, Alan Wilson, Sheila Morris); *North Bristol NHS Trust* (Mark Gompels, Sue Allan); *Leicester, University Hospitals of Leicester NHS Trust* (Adrian Palfreeman, Anne Moore, Lynn Fox, Josef Bojanowski, Adam Lewszuk); *Woolwich, South London Healthcare NHS Trust* (Stephen Kegg, Paul Main, Dr. Mitchell, Dr. Hunter), *UK Community Advisory Board* (Memory Sachikonye); *St. George's*

Healthcare NHS Trust (Phillip Hay, Mandip Dhillon); *York Teaching Hospital NHS Foundation Trust* (Fabiola Martin, Sarah Douglas, Sarah Russell-Sharpe).

Funding

The UK CHIC Study is funded by the Medical Research Council, UK (grant numbers G0000199, G0600337 and G0900274). The views expressed in this manuscript are those of the researchers and not necessarily those of the MRC.

Appendix C

UK HIV Kidney Transplant Study Group

Steering Committee

Esther Gathogo, Sanjay Bhagani, Marta Boffito, Martin Drage, Lisa Hamzah, Mark Harber, Rachel Hilton, Saye Khoo, Rachael Jones, Jeremy Levy, Neal Marshall, Graham Davies, Frank Post (PI)

Study Group

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Appendix D

Study Ethics Approval

NHS

National Research Ethics Service
Wrightington, Wigan & Leigh Research Ethics Committee

Room 181
Gateway House
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Manchester
M60 7LP

Telephone: 0161 237 2166
Facsimile: 0161 237 2383

22 May 2009

Miss Esther Nyanganyi-Gathogo
Pharmacy Department
Royal Free Hampstead Hospital
Pond Street
London
NW3 2QG

Dear Miss Nyanganyi-Gathogo

Full title of study: **The Safety and Outcomes of Immunosuppressant drug therapy in HIV positive kidney transplant patients.**
REC reference number: **09/H1014/36**

Thank you for your letter of 21 May 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Response to Request for Further Information		21 May 2009
Participant Information Sheet	2.0	21 May 2009
Investigator CV	Paul Wade	
Application	2.2	29 April 2009
Protocol	1	10 February 2009
Investigator CV	J. Farrell	29 April 2009
Investigator CV	E. Nyanganyi-Gathogo	29 April 2009
Participant Consent Form: Patient Consent Form (Royal Free Hampstead)	1.0	01 January 2009
Participant Consent Form: Participant Consent Form	1.0	01 March 2009
GP/Consultant Information Sheets	1.0	01 March 2009
Statistician Comments	1	05 March 2009
Copy of Information Governance Certificate	E. Nyanganyi-Gathogo	24 April 2009
Copy of Good Clinical Practice Certificate	E. Nyanganyi-Gathogo	09 May 2008

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review –guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1014/36	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Gary Young
Chair

Email: stephen.tebbutt@northwest.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mr John Farrell
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Appendix E

Study Centre List

UK HIV Kidney Transplant Study Centre List
Barts Health NHS Trust
Brighton and Sussex University Hospitals NHS Trust
Central Manchester University Hospitals
Chelsea and Westminster NHS Foundation Trust
East Kent Hospitals University NHS Foundation Trust
Eastbourne District General
Edinburgh, NHS Lothian
Epsom and St Helier University Hospitals
Garden Clinic Slough (HIV Centre)
Gloucestershire Royal Hospital
Guy's and St Thomas' NHS Foundation Trust
Heart of England NHS Foundation Trust, Birmingham
HIV Services Clinic and Community, The Hillingdon Hospital
Imperial College Healthcare NHS trust
King's College Hospital NHS Foundation Trust
Lancashire Care NHS Foundation Trust
Luton & Dunstable
Maidstone and Tunbridge Wells NHS Trust
Medway NHS Foundation Trust
Mid-Cheshire Hospitals NHS Foundation Trust
Monsall Unit, North Manchester Hospital
Mortimer Market Centre, University College London Hospitals
Newham University Hospital NHS Trust
NHS Greater Glasgow and Clyde
North Middlesex University Hospital NHS Trust
North West London Hospitals NHS Trust
Nottingham University Hospitals NHS Trust
Oxford Radcliffe Hospitals NHS Trust
Pennine Acute Hospitals NHS Trust, Manchester
Queen Elizabeth Hospital
Royal Berkshire NHS Foundation Trust
Royal Free London NHS Foundation Trust
Royal Liverpool & Broadgreen University Hospitals NHS Trust
Spire Manchester Hospital, Salford
St George's Healthcare Trust and St George's, University of London
University College London
University Hospitals Birmingham NHS Foundation Trust
University Hospitals of Leicester NHS Trust
University of Liverpool
West Middlesex University Hospital NHS Trust

Appendix F

Study Data Collection Form

HIV Kidney Transplantation Study

Demographics and Centre of Care

Patient Hospital No		Study ID	
Patient Initials		UK CHIC ID *(if applicable)*	
Patient DOB		Form completed by	
Ethnicity		Date form completed	
Gender		HIV Centre	
		Renal / Transplant Centre	

PRE-TRANSPLANT DATA

HIV Parameters

Date of HIV diagnosis		HIV Risk (i.e MSM, HTS)	
Baseline HIV VL (cps/ml)		CD4 nadir (cells/mm^3)	Date
Antiretroviral (ART) Start date		*Please specify ART history in **Appendix 1 A** *(if not UKCHIC site)*	

List ART at KT below

Drug Name	Start date	Stop date	Drug Name	Start date	Stop date

Renal Parameters

Aetiology of kidney disease (KD)

KD diagnosis confirmed by: Biopsy ☐ Radiology ☐ Other (specify)

Start dialysis date *(if applicable)* Dialysis history: HD ☐ PD ☐ Both HD & PD ☐

Pre-transplant trial of immunosuppressant (Y/N) If Y, specify details in **Appendix 1 B**

Co-morbidities & Co-infections at the time of Kidney Transplantation

Hepatitis B sAg		HBV DNA *(if applicable)*	
Hepatitis C Ab		HCV RNA level *(if applicable)*	
CMV IgG		CMV VL *(if applicable)*	
Diabetes		Hypertension	
Other co-morbidities			

Opportunistic infections (OI) pre-transplant? (Y/N) *If Y, specify details in **Appendix 1 C**

Tumours & Malignancies pre-transplant? *If Y, specify details in **Appendix 1 C**

POST-TRANSPLANT DATA

*Give details of immunosuppressant drug management in **Appendix 1 D** Weight at KT (kg) ☐ Height (m) ☐

Date of kidney transplant (KT) Is this first KT (Y/N) ☐

If N, specify details of previous transplants

Type of graft: Cadaveric donor ☐ Live donor ☐

Donor age (yr) ☐ Donor CMV IgG status *(if known)* ☐ HLA mismatch status

Other organ transplant (Y/N) ☐ If Y, specify details

Graft outcomes *(specify details in **Appendix 1 E**)* Acute rejection ☐ Chronic rejection ☐ Delayed graft function ☐

Post-transplant Infections & malignancies *(specify details in **Appendix 1 F**)* OIs ☐ Malignancies ☐ CMV nephropathy ☐ BK nephropathy ☐

Follow-up (FU)

Last FU date ☐ Outcome at FU: Alive ☐ Deceased ☐ Lost to FU ☐ Transferred care ☐

If deceased, indicate cause of death

Graft functioning (Y/N) ☐ If N, details and date graft loss

Kindly provide serial values (with dates) for the following parameters (preferably database/EPR downloads – any format):

CD4 ☐ Renal biopsies ☐ Immunosuppressant drug levels ☐

HIV VL ☐ Serum creatinine ☐ Antiretroviral drug info pre- & post-KT ☐

Appendix 1 (Use if no electronic records are available)

A. Antiretroviral Therapy (ART) [list history from when first diagnosed to current]

Drug Name	Start date	Stop date

Drug Name	Start date	Stop date

B. Pre-transplant Trial of Immunosuppression

Drug Name	Dose	Start date	Stop date

Drug Name	Concentration	Date

C. Pre-transplant Opportunistic Infections, Malignancies & Tumours

Diagnosis	Date of diagnosis

Diagnosis	Date of diagnosis

D. Post-transplant Immunosuppressant Drugs (inc monoclonal antibodies)

Drug Name	Dose	Start date	Stop date

Drug Name	Dose	Start date	Stop date

Concomitant medications [0-2months post-transplant only]

Drug Name	Dose	Start date	Stop date

Drug Name	Dose	Start date	Stop date

E. Post-transplant Rejection episodes

Acute / Chronic Rejection	Banff classification	Management / outcome	Biopsy proven (tick) *attach copy

F. Post-transplant Infections, malignancies & tumours

Diagnosis	Date of diagnosis

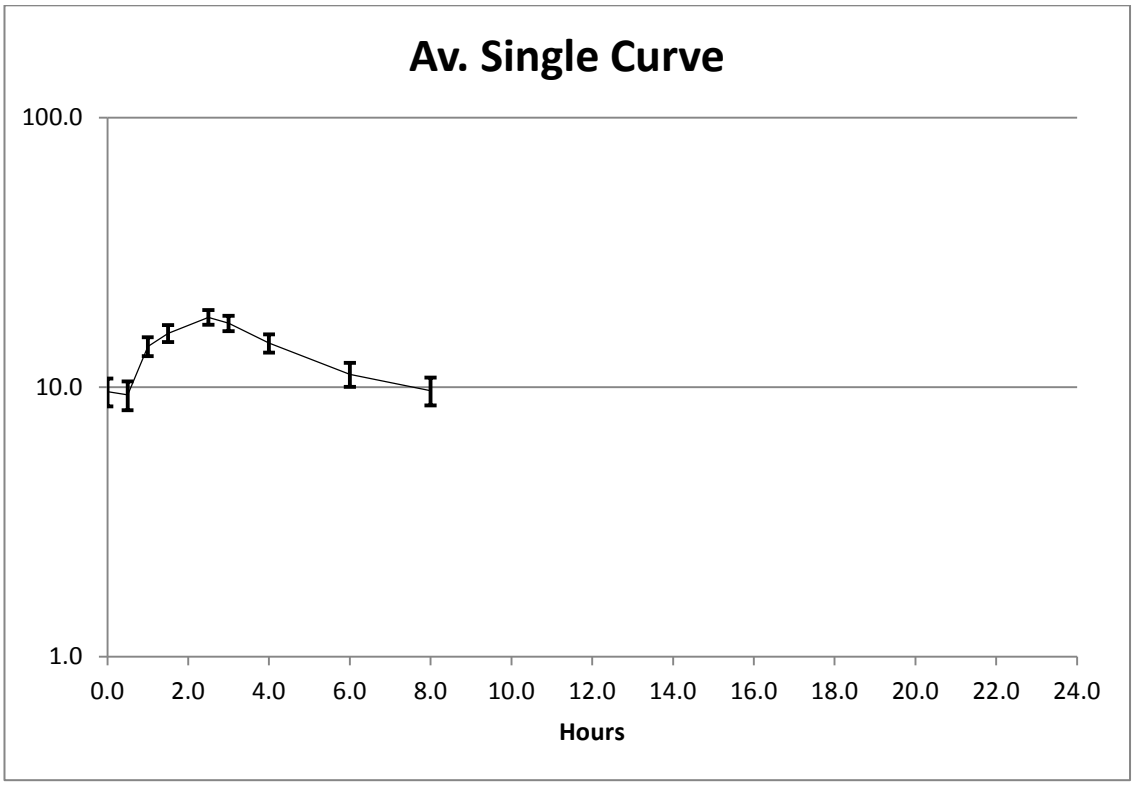
Diagnosis	Date of diagnosis

Appendix G

Pharmacokinetic Studies

After oral administration of TAC, whole blood concentration-time profile from 6 HIV/KT recipients were used to derive maximal drug concentration achieved (C_{max}), time to maximal concentration (T_{max}), and the area under the concentration-time curve (AUC). AUCs were calculated using the linear-log trapezoidal method.

Graph of average single curve of 6 patients in log scale with Standard Error Bars



Graph of superimposed AUC for 6 patients on cART at different time points post-HIT/KT

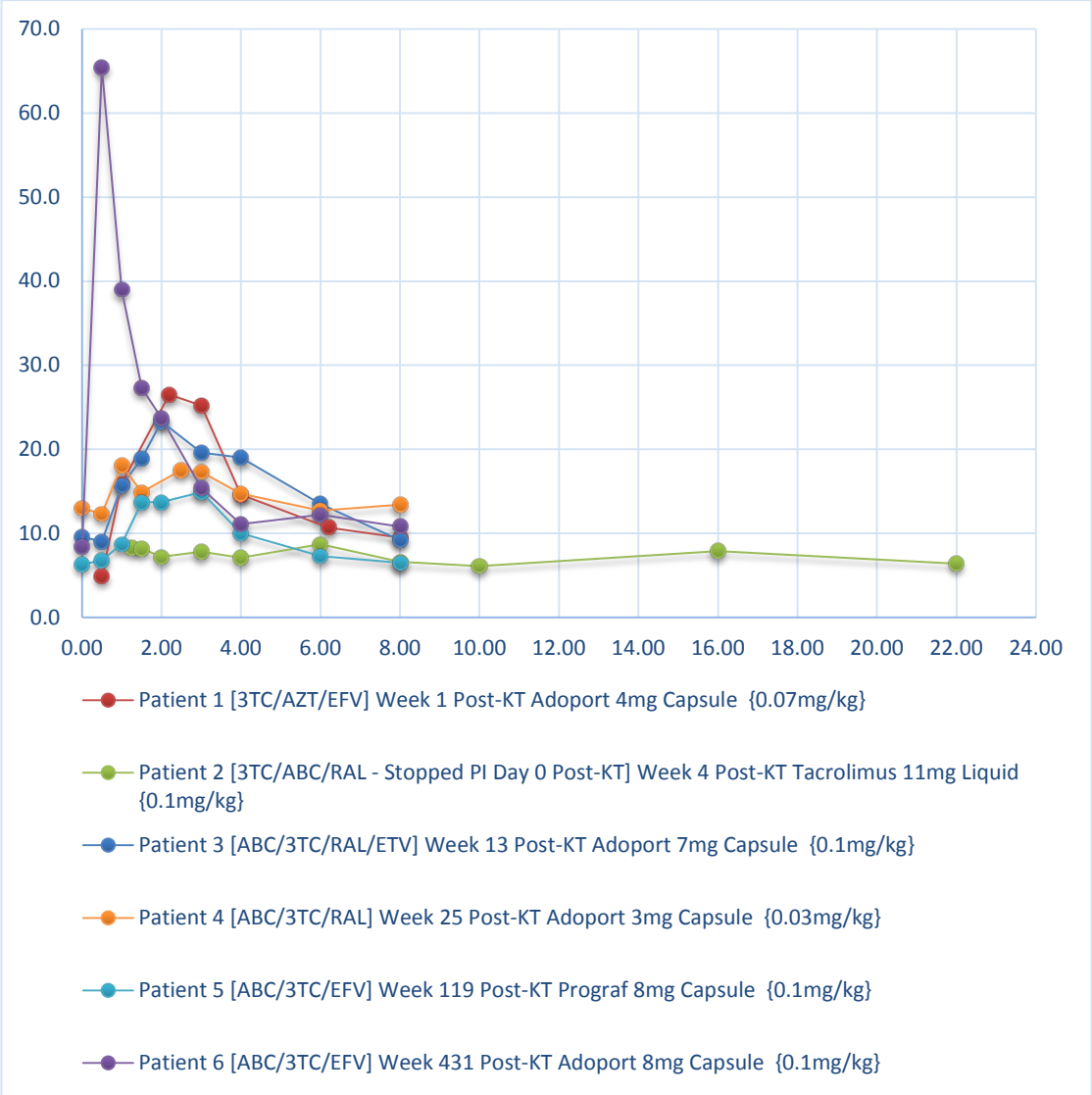


Table 41: Non-compartmental Pharmacokinetic Analysis - Calculated PK parameters using linear trapezoidal method

	HIV Negative Reference	USA Cohort**	USA Cohort**	USA Cohort**	USA Cohort**	Patient 1252	Patient 1257	Patient 1251	Patient 112001	Patient 1256
Week post-KT		2-12	28-104	2-12	28-104	1	13	25	120	431
cART	N/A	Tac+NVP	Tac+NVP	Tac+EFV	Tac+EFV	3TC/AZT/EFV	ABC/3TC/RAL/ETV	ABC/3TC/RAL	3TC/ABV/EFV	ABC/3TC/EFV
Tacrolimus PK Profile_Dose		variable	variable	variable	variable	4mg	7mg	3mg	8mg	8mg
Dose Frequency (hourly)						12	12	12	12	12
Weight (kg)						50	65	93	63	91
Weight normalised dose (mg/kg)						0.08	0.11	0.03	0.13	0.09
Ctrough (ng/ml) pre-AUC						5.2	9.6	13	6.3	8.4
Ctrough (ng/ml) post-AUC						5.1	8.3	16.4	5.1	NA
Cmax (ng/ml)						26.5	23.3	18.1	14.9	65.4
Tmax (hours)						2.2	2.0	1.0	3.0	0.5
Kel						0.1087	0.1813	0.0964	0.1077	0.3698
T1/2 (hours)						6.375344986	3.822393822	7.18879668	6.43454039	1.873985938
Conc. Time zero						3.0394	3.6766	3.1092	2.7003	3.8742
Vd (mL)						UD	177.1621523	133.9099511	537.4828329	166.1675839
Clearance (mL/hour)						UD	32.11949822	12.90891929	57.8869011	61.44877253
Time to steady state (hours) [5xT1/2]						31.88	19.11	35.94	32.17	9.37
AUC (ng*h/ml/mg/kg)	2000 - 5000	2170 (936-3261)	4220(2703-6229)	3644 (3115-5157)	1911(1423-3207)	1480.02875	1035.5	3885.8	774.5	1529.8

*UA – Unable to determine; Patient 1254 – excluded, not enough data points & on PI based cART Refer to graph; Note that the AUC in steady state equals AUC∞ after the first dose
**Reference: (PDRNetwork, 2011, Frassetto et al., 2013)

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